PATENT
ATTORNEY DOCKET NO.: 054945-0023

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,434,171	)
Granted: July 18, 1995	)
	)
Patentees: Scott A. FRANK *et al.*	)
	)
Assignee: Eli Lilly and Company	)
	)
FOR: PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYLCARBOXYLATES AND INTERMEDIATES	)

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window
MAIL STOP: HATCH-WAXMAN PTE
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Date **June 17, 2008**

FEE COVER SHEET FOR
APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

1. Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. § 156 including Exhibits 1-14 (Original + 2 sets).

2. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

3. Fee Calculation (37 C.F.R. §1.16)

Fee for Patent Term Extension	$ 1,120.00
Reduction by ½ for filing by a small entity	$ 0.00
TOTAL FEE =	$ 1,120.00

4. Fee Payment

☒ The Commissioner is hereby authorized to charge **$1,120.00** to Deposit Account No. 50-0310 for Extension of Term of Patent (37 C.F.R. §1.20(j)(1) (PTO Fee Code 111).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 17, 2008
By: _____
Donald J. Bird
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Date **June 17, 2008**

APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), Eli Lilly and Company (hereinafter "Applicant" or "Eli Lilly") hereby requests an extension of the patent term of United States Patent No. 5,434,171 (hereinafter variously referred to as "U.S. Patent No. 5,434,171" or "the '171 Patent").

Attention is called to the simultaneous filing by Applicant of a request for extension of the patent term of Applicant's United States Patent No. 5,250,542 based upon the same regulatory review period as the subject application, as authorized by 37 CFR § 1.785(b). It is understood that when these two patents are found to be eligible for patent term extension based on the same regulatory review period, that the final determination under 37 CFR § 1.750 will provide a period of

time for Applicant to elect the patent for which extension is desired, accompanied by an express withdrawal of the application for extension of the nonelected patent as provided in MPEP § 2761.

Applicant, Eli Lilly and Company, a corporation created and existing under the Laws of the State of Indiana, represents that it is the record owner of United States Patent No. 5,434,171, by reason of an assignment from the inventors thereof recorded on February 15, 1995 at Reel 007343, Frame 0467. A copy of the U.S. Patent and Trademark Office Abstract of Title confirming recordation of the Assignment is included in **Exhibit 1** hereto. The active moiety in the approved product that forms the basis for this application was initially developed at Eli Lilly (then designated as LY246736), and is exclusively licensed by Eli Lilly to Shire Pharmaceutical Group (formerly Roberts Pharmaceutical) under an agreement dated November 5, 1996 (including a license under U.S. Patent 5,434,171), and is exclusively sublicensed by Shire Pharmaceutical Group to Adolor Corporation under an option and license agreement dated June 10, 1998 (including a sublicense under U.S. Patent 5,434,171). The undersigned registered practitioner, Donald J. Bird (Reg. No. 25,323), is counsel for the marketing applicant (Adolor Corporation), and has been authorized to act on behalf of the patent owner (Eli Lilly) with respect to this Application and all correspondence pertaining thereto as set forth in section (15) below.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*, and follows the numerical sequence and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is ENTEREG® (alvimopan) capsules. The active moiety of the approved product has the chemical name:

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid,

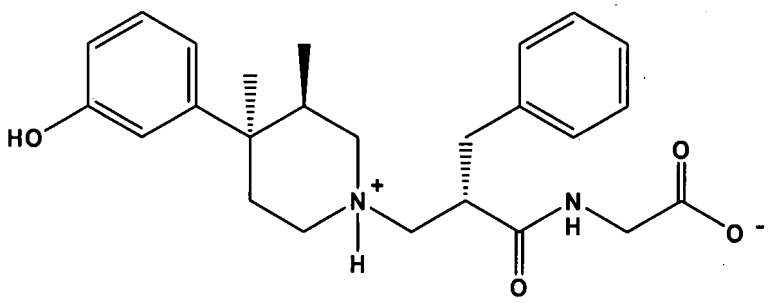
the molecular formula:

$C_{25}H_{32}N_2O_4$

a molecular weight of:

424.5;

and the structural formula:



and is present in the approved product in the dihydrate form, which has been assigned the USAN name of alvimopan. Alvimopan thus has the chemical name, as stated in Section 11 "Description" of the Approved Label (**Exhibit 2**):

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate

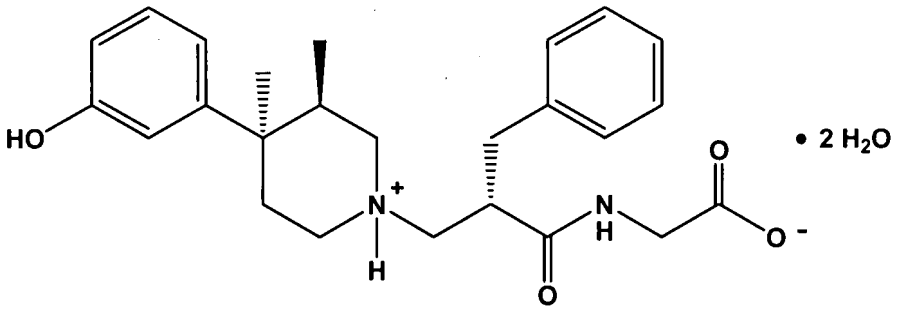
the molecular formula:

$C_{25}H_{32}N_2O_4 \bullet 2\ H_2O$

a molecular weight of:

460.6;

and the structural formula:



(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

ENTEREG® (alvimopan) Capsules was subject to regulatory review under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

ENTEREG® (alvimopan) Capsules received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355(b)) upon approval of NDA 21,775 on May 20, 2008.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of the product ENTEREG® Capsules is alvimopan, which has not been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act prior to approval of NDA 21,775 on May 20, 2008.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved on May 20, 2008, and the last day within the sixty day period permitted for submission of an application for patent term extension is July 19, 2008.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which an extension is being sought is as follows:

Inventors:	Scott A. Frank Douglas E. Prather Jeffrey A. Ward John A. Werner
U.S. Patent No.:	5,434,171
Earliest Filing Date:	December 8, 1993
Grant Date:	July 18, 1995
Expiration Date:	December 8, 2013

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A full copy of U.S. Patent No. 5,434,171, for which extension is being sought, is attached as **Exhibit 3**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of the maintenance fee statement showing timely payment of all maintenance fees when due is attached as **Exhibit 4**.

No disclaimer, certificate of correction or reexamination certificate has been filed and/or issued for U.S. Patent No. 5,434,171.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

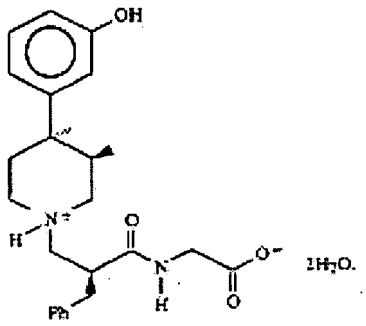
Claims of U.S. Patent No. 5,434,171 read on the approved product as detailed below.

Patent Claims to the Approved Product:

Claims 8, 9, 15 and 16 of U.S. Patent No. 5,434,171 encompass (read on) the approved product.

Claim 8 reads as follows:

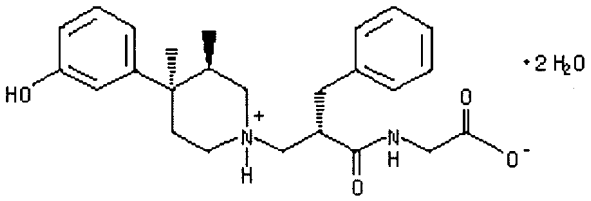
8. A crystalline dihydrate compound of the Formula 5



Claim 8 of U.S. Patent 5,434,171 reads on (encompasses) the approved product *per se*, more specifically:

As stated and illustrated in Section 11 "Description" of the Approved Label at lines 2-7, "[c]hemically, alvimopan is the single stereoisomer [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-

oxo-3-phenylpropyl]amino]acetic acid dihydrate. It has the following structural formula:



Alvimopan is a white to light beige powder with a molecular weight of 460.6, and the empirical formula is $C_{25}H_{32}N_2O_4 \bullet 2H_2O$." The approved product comprises a crystalline dihydrate compound of formula 5 as claimed in claim 8.

* * * * *

Claim 9 reads as follows:

9. A compound of claim 8 wherein the crystalline dihydrate compound is at least 97% (2S,3R,4R)dihydrate.

Claim 9 is dependent on claim 8 and reads on (encompasses) the approved product for the reasons stated above, and more specifically:

As stated in Section 11 "Description" of the Approved Label at lines 2-4, the crystalline dihydrate compound of the approved product is "the single stereoisomer [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate," *i.e.*, at least 97% (2S,3R,4R)dihydrate.

* * * * *

Claim 15 reads as follows:

15. A pharmaceutical formulation comprising an effective amount of a compound of claim 8 in combination with one or more pharmaceutically acceptable excipients.

Claim 15 is dependent on claim 8 and reads on (encompasses) the approved product for the reasons stated above, and more specifically:

As stated in Section 11 "Description" of the Approved Label at lines 11-12, "ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol."

* * * * *

Claim 16 reads as follows:

16. A formulation of claim 15 wherein the formulation is a hard gelatin capsule.

Claim 16 is dependent on claim 15 and reads on (encompasses) the approved product for the reasons stated above, and more specifically:

As stated in Section 3 "Dosage Forms and Strengths" of the Approved Label at lines 1-2, the dosage forms of the approved product are "hard gelatin capsules."

* * * * *

Patent Claims to the Method of Using the Approved Product:

Method claim 11 of U.S. Patent No. 5,434,171 encompasses (reads on) the approved product.

Claim 11 reads as follows:

11. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 8.

Method claim 11 is dependent on product claim 8, and reads on (encompasses) the approved product for the reasons stated with respect to claim 8 and additionally:

As stated in Section 11 "Description" of the Approved Label at lines 1-2, "ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist." The Approved Label additionally notes in Section 12.1 "Mechanism of Action" at lines 19-21 that "[f]ollowing oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors."

* * * * *

Patent Claims to the Method of Manufacturing the Approved Product:

No claims of U.S. Patent No. 5,434,171 are directed toward a method of manufacturing the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The IND application for LY246736 Dihydrate Capsules was submitted to the FDA by Eli Lilly on October 11, 1993. By letter dated October 18, 1993, the FDA acknowledged receipt of the IND application on October 12, 1993, and assigned IND number 43,693, resulting in an IND effective date of November 11, 1993. A copy of this FDA acknowledgment letter is attached as **Exhibit 5**.

On November 5, 1996, Eli Lilly entered into a License Agreement with Roberts Laboratories Inc., a wholly owned subsidiary of Roberts Pharmaceutical Corporation (hereinafter collectively referred to as "Roberts"), granting Roberts the exclusive right to develop and commercialize LY246736, including a license under U.S. Patent 5,434,171. Effective February 1, 1997, Eli Lilly transferred sole sponsorship of IND 43,693 to Roberts, and notified the FDA by letter of February 3, 1997, a copy of which is attached as **Exhibit 6**.

On June 10, 1998, Adolor entered into an option and license agreement with Roberts (now Shire Pharmaceutical Group) under which Adolor is exclusively sublicensed to all rights of Shire with respect to LY246736, including a sublicense under U.S. Patent 5,434,171. On August 3, 1998, Adolor filed an IND application for the investigational drug ADL 8-2698 (Adolor's name for LY246736), which was assigned IND number 56,553. By letters dated June 24, 1998 and June 17, 1999, Roberts authorized the FDA to refer to IND 43,693 on behalf of Adolor Corporation (copies attached as **Exhibits 7 and 8**), and by letter to the FDA dated March 22, 2000, Roberts transferred all rights to IND 43,693 to Adolor (copy attached as **Exhibit 9**). Prior to this transfer on March 22, 2000,

Roberts withdrew IND 43,693 by letter to the FDA of December 3, 1999, noting that the investigational drug has been licensed to Adolor Corporation, and will be researched under the Adolor Corporation's IND application. By letter dated September 21, 2000 (copy attached as **Exhibit 10**), Adolor provided the FDA with requested information regarding the transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, noting that the investigational compound LY236736 Dihydrate Capsules was licensed to Adolor for development, that Adolor filed its own IND 56,553, that Adolor's IND 56,553 was currently active and refers to the investigational drug as ADL 8-2698, that Roberts' (formerly Lilly's) IND 43,693 was referenced in Adolor's IND filing, and that any relevant sections and reports from IND 43,693 will be filed in the NDA.

Thus, although Adolor has conducted all clinical studies under IND 56,553, Adolor has used IND 43,693 as reference, and has submitted relevant sections and reports from IND 43,693 in the NDA. Under these circumstances, the "regulatory review period" under 35 U.S.C. § 156(g)(1) began on **November 11, 1993**, the effective date of IND 43,693.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The final reviewable unit constituting the complete NDA 21,775 for ENTEREG® was initially submitted to the FDA on June 25, 2004. The FDA acknowledged that the final reviewable unit of the complete NDA was received on June 25, 2004, as confirmed by FDA letter dated September 7, 2004, (copy attached as **Exhibit 11).** This establishes June 25, 2004 as the initial submission date of the NDA for the approved product for purposes of 35 U.S.C. 156(g)(1).

(C) The date on which the NDA was approved or the Product License issued.

The NDA was approved by the FDA approval letter sent May 20, 2008, setting the effective date of the approval as the May 20, 2008 date of the letter. A copy of this five-page FDA approval letter plus the dated electronic signature page is attached as **Exhibit 12.** This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(1) as May 20, 2008.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The significant activities undertaken by the marketing applicant with respect to the approved product during the applicable regulatory review period commenced with the submission by Lilly of an Investigational New Drug Application (IND) on October 11, 1993 for Compound LY246736 Dihydrate Capsules, which was assigned IND number 43,693. As detailed in answer to question (10)(i)(A) above, on November 5, 1996, Lilly entered into an agreement with Roberts, granting Roberts the rights to development of LY246736 Dihydrate Capsules. Effective February 1, 1997, Lilly transferred sole sponsorship of IND 43,693 to Roberts, and so notified the FDA by letter of February 3, 1997. By agreement dated June 10, 1998, Adolor entered into an Option and License Agreement with Roberts for a sublicense of all rights to the development and commercialization of LY246736, and on August 3, 1998, Adolor filed an IND application for the investigational drug ADL 8-2698 (Adolor's name for LY246736), which was assigned IND number 56,553. By letters dated June 24, 1998 and June 17, 1999, Roberts authorized the FDA to refer to IND 43,693 on behalf of Adolor Corporation, and by letter of dated March 22, 2000, Roberts transferred all rights to IND 43,693 to Adolor. Prior to this transfer on March 22, 2000, Roberts withdrew IND 43,693 by letter to the FDA of December 3, 1999, noting that the investigational drug has been licensed to Adolor, and will be researched under Adolor's IND application. Adolor's letter to the FDA of September 21, 2000, provided further information on the transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, and made clear that LY236736 Dihydrate Capsules had been licensed to Adolor for development, that Adolor filed its own IND 56,553, that Adolor's IND 56,553 was currently active and refers to the investigational drug as ADL 8-2698, that IND 43,683 was referenced in Adolor's IND filing, and that any relevant sections and reports from IND 43,693 will be filed in the NDA. Although Adolor has conducted all clinical

studies under IND 56,553, Adolor has used IND 43,693 as reference, and has submitted relevant sections and reports from IND 43,693 in NDA 21,775.

Because of the complexities created by the circumstances and filings surrounding the transfers of IND 43,693, rights of reference thereto, and rights to the underlying compound LY245736 (ADL 8-2698 and later alvimopan) from Lilly to Roberts and then to Adolor, and the overlapping time period of studies done by Adolor under its IND 56,553, a Chronological Listing of Significant Activities during the testing phase under these two INDs and during the approval phase under NDA 21,775 is attached as **Exhibit 13**, the contents of which are incorporated herein by reference as providing a brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the Approved Product.

The regulatory review period for ENTEREG® (alvimopan) Capsules ended with permission for commercial marketing being granted by the FDA on May 20, 2008.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Statement That The Patent Is Eligible For Extension

Applicant is of the opinion that U.S. Patent No. 5,434,171 is eligible for extension under 35 U.S.C. 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent No. 5,434,171 claims the approved product, as detailed in section (9) above.

(2) 35 U.S.C. 156(a)(1)

U.S. Patent No. 5,434,171 granted on an earliest filed U.S. application filed on December 8, 1993 and there are no terminal disclaimers. As such, the patent expires on December 8, 2013. This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is being submitted by Eli Lilly and Company as the owner of record of No. 5,434,171 (through an assignment from the inventors recorded February 15, 1995 at Reel 007343, Frame 0467), in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the May 20, 2008 approval letter from the FDA (**Exhibit 12**), ENTEREG® (alvimopan) Capsules was subject to a regulatory review period under Section 505(b) of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of ENTEREG® (alvimopan) Capsules after this regulatory review period is the first permitted commercial marketing of ENTEREG® (alvimopan) Capsules under provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) under which the regulatory review period occurred, as confirmed by the absence of any approved NDA for the approved product prior to May 20, 2008.

(7) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the product ENTEREG® (alvimopan) Capsules.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,434,171 should be extended by **1826 days**, from December 8, 2013 to **December 8, 2018**. In accordance with the implementing regulations of 37 C.F.R. 1.175 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 5,434,171 based on the regulatory review for ENTEREG® was determined as follows:

Sec. 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.

(a) If a determination is made pursuant to Sec. 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as

calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (Sec. 1.321).

U.S. Patent 5,434,171 issued on July 18, 1995, from an earliest filed U.S. application filed on December 8, 1993. Pursuant to 35 U.S.C. 154(c), this patent is entitled to an original term of 20 years from December 8, 1993, which provides an original expiration date of **December 8, 2013**.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of--

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of IND 43,693 on November 11, 1993 to the filing of NDA 21,775 on June 25, 2004, being **3880 days**.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of NDA 21,775 on June 25, 2004 to the date of approval of NDA 21,775 on May 20, 2008, being **1426 days**.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being **5306 days**.

(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;

With respect to paragraph (d)(1)(i), **614 days** of the periods of paragraphs (c)(1) and (c)(2) were before the July 18, 1995 date on which original U.S. Patent 5,434,171 issued.

With respect to paragraph (d)(1)(ii), 35 U.S.C. 156(d)(2)(B) provides that if a petition is submitted to the Secretary not later than 180 days after publication of the determination of the applicable regulatory review period, upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall determine if the applicant acted with due diligence during the applicable regulatory review period. The Secretary making this determination shall notify the Director of the determination and shall publish in the Federal Register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such a request is made within such period, the Secretary shall hold such hearing, and shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, the Secretary shall affirm or revise the

determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register. There has been no such petition or determination by the Secretary, and thus the number of days under (d)(1)(ii) is **0 days**.

With respect to paragraph (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) is one-half of (3880-614-0=3266) days, which is **1633 days** (ignoring the half day).

Subtracting from the regulatory review period of 5306 days as determined above pursuant to section 1.175(c) the number of days determined above with respect to paragraphs (d)(1)(i), (ii) and (iii), the term of patent extension is **5306 days** minus **614 days** minus **0 days** minus **1633 days** for a sum total of **3059 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 5,434,171 is December 8, 2013 and is not shortened by terminal disclaimer. Adding the 3059 days determined in paragraph (d)(1) to the original term of the patent results in an extended term to **April 24, 2022.**

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the May 20, 2008 date of the approval of the NDA results in the date May 20, 2022.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier of April 24, 2022 and May 20, 2022 is **April 24, 2022**.

(5) If the original patent was issued after September 24, 1984,
(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and
(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The original patent issued after September 24, 1984. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of December 8, 2013 gives a date of **December 8, 2018**. The earlier of April 24, 2022 and December 8, 2018 is **December 8, 2018**.

(6) If the original patent was issued before September 24, 1984, and
(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--
(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and
(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or
(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--
(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer, and
(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

Since U.S. Patent 5,434,171 issued after September 24, 1984, no further adjustment to the extended term of December 8, 2018 is required.

Thus, as calculated above, the term of U.S. Patent No. 5,434,171 is eligible for a **1826 day extension to December 8, 2018**.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)).

As noted in the letter of transmittal submitted with this application, the Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 50-0310.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please address all inquiries and correspondence relating to this application for patent term extension to the following registered practitioner, who is counsel for the marketing applicant and authorized to act on behalf of the patent owner with respect to this Application and all correspondence pertaining hereto:

Donald J. Bird
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: 202-739-5320
Facsimile: 202-739-3001

A copy of the Authorization to Act is attached as **Exhibit 14**.

Respectfully Submitted,
Morgan, Lewis & Bockius LLP

Date: June 17, 2008 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

LIST OF EXHIBITS

Exhibit No.	Ref. Pages	Description
1	2	US PTO Assignment of Frank Patent from inventors to Eli Lilly, recorded February 15, 1995 at Reel 007343, Frame 0467.
2	3	Approved Label for ENTEREG™ (alvimopan) capsules.
3	5	U.S. Patent No. 5,434,171 to Frank et al.
4	5	Maintenance Fee Statement as of June 2, 2008 in U.S. Patent No. 5,434,171 to Frank et al., showing that all maintenance fees have been paid.
5	10	FDA letter dated October 18, 1993 acknowledging receipt of IND application on October 12, 1993, and assigning IND number 43,693.
6	10	Eli Lilly Letter of February 3, 1997 notifying FDA of transfer of sole sponsorship of IND 43,693 to Roberts, effective February 1, 1997.
7	10	Roberts letter dated June 24, 1998 authorizing FDA to refer to IND 43,693 on behalf of Adolor Corporation.
8	10	Roberts letter dated June 17, 1999 authorizing FDA to refer to IND 43,693 on behalf of Adolor Corporation.
9	10	Roberts letter dated March 22, 2000 notifying FDA of transfer of all rights to IND 43,693 to Adolor.
10	11	Adolor letter dated September 21, 2000 providing FDA with requested information regarding the transfer of sponsorship of IND 43,693 from Roberts to Adolor.
11	11	FDA letter dated September 7, 2004 acknowledging receipt of the final reviewable unit constituting the complete Adolor NDA on June 25, 2004.
12	12, 16	Five-page FDA approval letter (with dated electronic signature page) under NDA Number 21,775 dated May 20, 2008.
13	14	Chronological Listing of Significant Activities under IND 43,693, IND 56,553 and NDA 21,775.
14	22	Authorization to Act on Behalf of Assignee-Patent Owner.

EXHIBIT 1

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 5434171 **Issue Dt:** 07/18/1995 **Application #:** 08164074 **Filing Dt:** 12/08/1993

Inventors: SCOTT A. FRANK, DOUGLAS E. PRATHER, JEFFREY A. WARD, JOHN A. WERNER

Title: PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYLCARBOXYLATES AND INTERMEDIATES

Assignment: 1

Reel/Frame: 007343/0467 **Recorded:** 02/15/1995 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: FRANK, SCOTT A. **Exec Dt:** 12/08/1993

PRATHER, DOUGLAS E. **Exec Dt:** 12/08/1993

WARD, JEFFREY A. **Exec Dt:** 12/08/1993

WERNER, JOHN A. **Exec Dt:** 12/08/1993

Assignee: ELI LILLY AND COMPANY PATENT DIVISION/MVJ
LILLY CORPORATE CENTER
INDIANAPOLIS, INDIANA 46205

Correspondent: CHERYL EYED
ELI LILLY AND COMPANY
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Search Results as of: 06/02/2008 11:02 AM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.0.1
Web interface last modified: April 20, 2007 v.2.0.1

RECORDATION FORM COVER SHEET
PATENTS ONLY

Attny Docket No. X-8847

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof:

1. Name of conveying party(ies):

Scott A. Frank
Douglas E. Prather
Jeffrey A. Ward
John A. Werner

Additional name(s) of conveying party(ies) attached? ( ) Yes (X) No

2. Name & address of receiving party(ies):

Name: Eli Lilly and Company
Patent Division/MVJ

Street Address: Lilly Corporate Center

City: Indianapolis State: IN Zip: 46205

3. Nature of conveyance:

(X) Assignment ( ) Merger
( ) Security Agreement ( ) Change of Name
( ) Other_____
Execution Date: December 8, 1993

Additional name(s) & address(es) attached?

( ) Yes (X) No

4. Application number(s) or patent Number(s):

If this document is being filed together with a new application, the execution date of the application is:_____

A. Patent Application No.(s):
08/164,074

B. Patent No.(s):

Additional Numbers attached ( ) Yes (X) No

5. Name and address of party to whom correspondence concerning documents should be mailed:

Cheryl Eyed
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

6. Total number of applications and patents involved: (1)

7. Total fee (37 CFR 3.41): $ 40.00
($40.00 per assignment)

( ) Enclosed
(X) Authorized to be charged to deposit account

8. Deposit account number: 05-0830

(attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

SC13099 03/06/95 08164074 05-0830 130 581 40.00CH

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

MaCharri R. Vorndran-Jones — MCharri R. Vorndran-J — 2/10/95
Name of Attorney Signing — Signature — Date

Total number of pages including cover sheet, attachments and document: (2)

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.

ELI LILLY AND COMPANY

BY Cheryl J. Eyed DATE 2-10-95

93752553

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

Rev. 8/93

Docket No. X-8847

ASSIGNMENT

WHEREAS we, Scott A. Frank, of the City of Lebanon, County of Boone, State of Indiana, and Douglas E. Prather, of the City of Brownsburg, County of Hendricks, and State of Indiana, and Jeffrey A. Ward, of the City of Indianapolis, County of Marion, and State of Indiana, and John A. Werner, of the City of Indianapolis, County of Marion, and State of Indiana

have made an invention which is the subject of an application for Letters Patent of the United States ("Application") entitled PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYLCARBOXYLATES AND INTERMEDIATES

which has been executed by us on the 8th day of December, 1993; and

WHEREAS ELI LILLY AND COMPANY, an Indiana corporation having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

NOW, THEREFORE, in consideration of the sum of one dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, we hereby sell, assign, transfer and set over unto Eli Lilly and Company, its successors and assigns (collectively "Lilly") our entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all Letters Patent of the United States and of all other countries which may be granted for such inventions, or any of them, all such inventions and all rights in such Application and Letters Patent to be held and enjoyed by Lilly for its own use and enjoyment to the full end of the term or terms for which such Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by us had this assignment and sale not been made.

We authorize and request the Commissioner of Patents and Trademarks of the United States to issue any such Letters Patent which may be granted on this Application to Lilly as assignee of the entire right, title and interest therein and thereto.

For ourselves and for our legal representatives, we covenant and agree with Lilly that we have not granted to any others any license to make, use or sell any of such inventions, that our right, title and interest in such inventions has not been encumbered, that we have good right and title to sell and assign the same, and that we will not execute any instrument in conflict herewith.

For ourselves and for our heirs, successors and legal representatives, we further covenant and agree with Lilly that upon request we and they will: (i) execute continuing, divisional, or reissue applications, amended specifications, or rightful declarations or oaths; (ii) communicate to Lilly any facts known to us or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any interference proceedings or litigation; (iv) execute and deliver any application papers, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent, without further consideration than that now paid but at the expense of Lilly.

IN WITNESS WHEREOF we have executed this assignment on the 8th day of December, 1993.

Scott A. Frank

Jeffrey A. Ward

Douglas E. Prather

John A. Werner

UNITED STATES OF AMERICA

STATE OF INDIANA)
) ss:
COUNTY OF MARION)

December 8, 1993

Before me, a Notary Public for Marion County, State of Indiana, personally appeared Scott A. Frank, Douglas E. Prather, Jeffrey A. Ward, and John A. Werner, and acknowledged the execution of the foregoing instrument this 8th day of December, 1993.

JoEllen Conover
Notary Public

My commission expires:

JoELLEN CONOVER
MY COMMISSION EXPIRES
DECEMBER 5, 1996
RESIDENCE: MARION COUNTY

RECORDED
PATENT & TRADEMARK OFFICE
FEB 15 95

REEL 7343 FRAME 168

EXHIBIT 2

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTEREG safely and effectively. See full prescribing information for ENTEREG.

ENTEREG® (alvimopan) Capsules
Initial U.S. Approval: 2008

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.™) program may use ENTEREG.

INDICATIONS AND USAGE

ENTEREG is a peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. (1)

DOSAGE AND ADMINISTRATION

12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 12 mg (3)

CONTRAINDICATIONS

Therapeutic doses of opioids for more than 7 consecutive days prior to ENTEREG (4)

WARNINGS AND PRECAUTIONS

- A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo in a 12-month study in patients treated with opioids for chronic pain, although a causal relationship has not been established. (5.1)
- Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea. (5.3)
- Not recommended in patients with severe hepatic impairment. (5.4)
- Not recommended in patients with end stage renal disease. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3% and ≥1% placebo) in patients undergoing bowel resection were anemia, dyspepsia, hypokalemia, back pain, and urinary retention. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Adolor Corporation at 1-866-4ADOLOR (1-866-423-6567) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Patients with mild-to-moderate hepatic impairment do not require dosage adjustment, but they should be monitored for adverse effects. ENTEREG is not recommended for patients with severe hepatic impairment.(8.5)
- Renal impairment: Alvimopan has not been studied in patients with end stage renal disease. ENTEREG is not recommended for use in these patients. Dosage adjustment is not required in patients with mild to severe renal impairment but they should be monitored for adverse effects. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: May 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.) program may use ENTEREG. *[see Warnings and Precautions (5.1 and 5.2)]*

1 INDICATIONS AND USAGE

ENTEREG is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

For hospital use only. The recommended adult dosage of ENTEREG is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. Patients should not receive more than 15 doses of ENTEREG.

2.2 Special Populations

Geriatric Use: No dosage adjustment is necessary in elderly patients *[see Use in Specific Populations (8.4)]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild-to-moderate hepatic impairment (Child-Pugh Class A and B). ENTEREG is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*.

Renal Impairment: No dosage adjustment is necessary in patients with mild-to-severe renal impairment, but they should be monitored for adverse effects. ENTEREG is not recommended for use in patients with end-stage renal disease. *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

12 mg blue, hard gelatin capsules with "ADL2698" printed on both the body and the cap of the capsule.

4 CONTRAINDICATIONS

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Infarction in a 12 Month Study in Patients treated with Opioids for Chronic Pain

There were more reports of myocardial infarctions in patients treated with alvimopan

0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. In this study, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies in patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. A causal relationship with alvimopan has not been established.

5.2 Distribution Program for ENTEREG

ENTEREG is available only to hospitals that enroll in the E.A.S.E. program. To enroll in the E.A.S.E. program, the hospital must acknowledge that:

-hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use;
-patients will not receive more than 15 doses of alvimopan; and
-ENTEREG will not be dispensed to patients after they have been discharged from the hospital.

Contact the E.A.S.E. program at 1-866-4ADOLOR (1-866-423-6567).

5.3 Opioid Tolerance and Gastrointestinal-Related Adverse Effects

Patients recently exposed to opioids are expected to be more sensitive to the effects of μ-opioid receptor antagonists. Since ENTEREG acts peripherally, clinical signs and symptoms of increased sensitivity would likely be limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea). Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials; therefore, ENTEREG 12 mg capsules should be administered with caution to these patients.

5.4 Severe Hepatic Impairment

In patients with severe hepatic impairment, there is a potential for 10-fold higher plasma levels of drug *[see Clinical Pharmacology (12.3)]*. There are no studies of ENTEREG in patients with severe hepatic impairment undergoing bowel resection. Because of the limited data available, ENTEREG is not recommended for use in patients with severe hepatic impairment.

5.5 End-Stage Renal Disease

No studies have been conducted with end-stage renal disease. ENTEREG is not recommended for use in these patients.

5.6 Bowel Obstruction

Use of ENTEREG in patients undergoing surgery for correction of complete bowel obstruction is not recommended.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to ENTEREG in 1,650 patients in 9 placebo-controlled studies worldwide. The population was 19 to 97 years old, 68% were female, and 83% were Caucasian; 61% were undergoing bowel resection surgery. The first dose of ENTEREG was administered 30 minutes to 5 hours before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment).

Table 1 presents treatment-emergent adverse reactions reported in ≥3% patients treated with ENTEREG and for which the rate for ENTEREG was ≥1% than placebo. Treatment-emergent adverse reactions are those events occurring after the first dose of study medication treatment and within 7 days of the last dose of study medication or those events present at baseline that increased in severity after the start of study medication treatment.

Table 1. Treatment-Emergent Adverse Reactions That Were Reported in ≥3% of Either Bowel Resection Patients Treated With ENTEREG or All Surgical Patients Treated With ENTEREG and for Which the Rate for ENTEREG Was ≥1% Than Placebo

	Bowel Resection Patients		All Surgical Patients	
System Organ Class	Placebo (n = 986) %	ENTEREG (n = 999) %	Placebo (n = 1,365) %	ENTEREG (n = 1,650) %
Blood and lymphatic system disorders				
Anemia	4.2	5.2	5.4	5.4
Gastrointestinal disorders				
Constipation	3.9	4.0	7.6	9.7
Dyspepsia	4.6	7.0	4.8	5.9
Flatulence	4.5	3.1	7.7	8.7
Metabolism and nutrition disorders				
Hypokalemia	8.5	9.5	7.5	6.9
Musculoskeletal and connective tissue disorders				
Back pain	1.7	3.3	2.6	3.4
Renal and urinary disorders				
Urinary retention	2.1	3.2	2.3	3.5

7 DRUG INTERACTIONS

7.1 Potential for Drugs to Affect Alvimopan Pharmacokinetics

Based on *in vitro* data, alvimopan is not a substrate of CYP enzymes. Therefore, concomitant administration of ENTEREG with inducers or inhibitors of CYP enzymes is unlikely to alter the metabolism of alvimopan. No clinical studies have been performed to assess the effect of concomitant administration of inducers or inhibitors of cytochrome P450 enzymes on alvimopan pharmacokinetics.

In vitro studies suggest that alvimopan and its 'metabolite' are substrates for p-glycoprotein. A population PK analysis did not reveal any evidence that alvimopan or 'metabolite' pharmacokinetics were influenced by concomitant medications that are mild-to-moderate p-glycoprotein inhibitors. No clinical studies of concomitant administration of alvimopan and strong inhibitors of p-glycoprotein (e.g., verapamil, cyclosporine, amiodorone, itraconazole, quinine, spirinolactone, quinidine, diltiazem, bepridil) have been conducted.

A population PK analysis suggests that the pharmacokinetics of alvimopan were not affected by concomitant administration of acid blockers or antibiotics. However, plasma concentrations of the 'metabolite' were lower in patients receiving acid blockers or preoperative oral antibiotics (49% and 81%, respectively). Because the 'metabolite' is not required for efficacy, no dosage adjustments are necessary in these patients.

7.2 Potential for Alvimopan to Affect the Pharmacokinetics of Other Drugs

Alvimopan and its 'metabolite' are not inhibitors of CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 *in vitro* at concentrations far in excess of those observed clinically. Alvimopan and its 'metabolite' are not inducers of CYP 1A2, 2B6, 2C9, 2C19 and 3A4. *In vitro* studies also suggest that alvimopan and its 'metabolite' are not inhibitors of p-glycoprotein. These *in vitro* findings suggest that ENTEREG is unlikely to alter the pharmacokinetics of coadministered drugs through inhibition or induction of CYP enzymes or inhibition of p-glycoprotein.

Coadministration of alvimopan does not appear to alter the pharmacokinetics of morphine and its metabolite, morphine-6-glucuronide, to a clinically significant degree when morphine is administered intravenously. Dosage adjustment for intravenously administered morphine is not necessary when it is coadministered with alvimopan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in pregnant rats at about 68 to 136 times the recommended human oral dose based on the body surface area and intravenous doses of about 3.4 to 6.8 times the recommended human oral dose based on the body surface area and in pregnant rabbits at intravenous doses at about 5 to 10 times the recommended human oral dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Nursing Mothers

Alvimopan and its 'metabolite' are detected in the milk of lactating rats. It is not known whether alvimopan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENTEREG is administered to a nursing woman.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

Of the total number of patients in 5 clinical efficacy studies treated with ENTEREG or placebo, 45% were 65 years of age and over, while 18% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment based on increased age is required *[see Clinical Pharmacology (12.3)]*.

8.5 Hepatic Impairment

Although there is a potential for higher plasma levels of drug in patients with mild-to-moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*, dosage adjustment in these patients is not required. Patients with mild-to-moderate hepatic impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur. ENTEREG is not recommended for use in patients with severe hepatic impairment. *[See Dosage and Administration (2.2), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]*

8.6 Renal Impairment

Alvimopan has not been studied in patients with end-stage renal disease and ENTEREG is not recommended for use in these patients. Patients with mild-to-severe renal impairment do not require dosage adjustment, but they should be monitored for adverse effects. *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Patients with severe impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur.

9 DRUG ABUSE AND DEPENDENCE

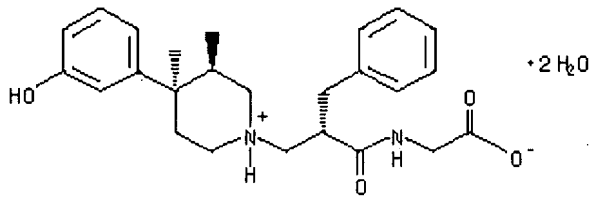
ENTEREG has no known potential for abuse or dependence.

10 OVERDOSAGE

There is no specific antidote for overdosage with ENTEREG. Patients should be managed with appropriate supportive therapy. Single doses up to 120 mg and multiple doses up to 48 mg for 7 days have been administered to normal, healthy subjects in clinical studies and were well tolerated.

11 DESCRIPTION

ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist. Chemically, alvimopan is the single stereoisomer [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate. It has the following structural formula:



Alvimopan is a white to light beige powder with a molecular weight of 460.6, and the empirical formula is $C_{25}H_{32}N_2O_4 \bullet 2H_2O$. It has a solubility of <0.1 mg/mL in water or buffered solutions between pH 3.0 and 9.0, 1 to 5 mg/mL in buffered solutions at pH 1.2, and 10 to 25 mg/mL in aqueous 0.1 N sodium hydroxide. At physiological pH, alvimopan is zwitterionic, a property that contributes to its low solubility.

ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alvimopan is a selective antagonist of the cloned human μ-opioid receptor with a Ki of 0.4 nM (0.2 ng/mL) and no measurable opioid-agonist effects in standard pharmacologic assays. The dissociation of [^{3}H]-alvimopan from the human μ-opioid receptor is slower than that of other opioid ligands, consistent with its higher affinity for the receptor. At concentrations of 1 to 10 μM, alvimopan demonstrated no activity at any of over 70 non-opioid receptors, enzymes, and ion channels.

Postoperative ileus is the impairment of gastrointestinal motility after intra-abdominal surgery or other non-abdominal surgeries. Postoperative ileus affects all segments of the gastrointestinal tract and may last from 5 to 6 days, or even longer. This may potentially delay gastrointestinal recovery and hospital discharge until its resolution. It is characterized by abdominal distention and bloating, nausea, vomiting, pain, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation. Postoperative ileus is the result of a multifactorial process that includes inhibitory sympathetic input, release of hormones, neurotransmitters, and other mediators (e.g., endogenous opioids). A component of postoperative ileus also results from an inflammatory reaction and the effects of opioid analgesics. Morphine and other μ-opioid receptor agonists are universally used for the treatment of acute postsurgical pain; however, they are known to have an inhibitory effect on gastrointestinal motility and may prolong the duration of postoperative ileus.

Following oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors. The antagonism produced by alvimopan at opioid receptors is evident in isolated guinea pig ileum preparations where alvimopan competitively antagonizes the effects of morphine on contractility. Alvimopan achieves this selective gastrointestinal opioid antagonism without reversing the central analgesic effects of μ-opioid agonists.

12.2 Pharmacodynamics

In exploratory studies in healthy volunteers, alvimopan 3 mg three times daily appeared to reduce the delay in gastrointestinal transit produced by morphine 30 mg twice daily as measured by radio-opaque markers.

In a study designed to evaluate potential effects on cardiac conduction, alvimopan did not cause clinically significant QTc prolongation at doses up to 24 mg twice daily for 7 days. The potential for QTc effects at higher doses has not been studied.

12.3 Pharmacokinetics

Following oral administration of alvimopan, an amide hydrolysis compound is present in the systemic circulation, which is considered a product exclusively of intestinal flora metabolism. This compound is referred to as the 'metabolite'. It is also a μ-opioid receptor antagonist with a Ki of 0.8 nM (0.3 ng/mL).

Absorption: Following oral administration of ENTEREG capsules in healthy volunteers, plasma alvimopan concentration peaked at approximately 2 hours postdose. No significant accumulation in alvimopan concentration was observed following twice daily (BID) dosing. The mean peak plasma concentration was 10.98 (±6.43) ng/mL and mean $AUC_{0\text{-}12h}$ was 40.2 (±22.5) ng•h/mL after dosing of alvimopan at 12 mg BID for 5 days. The absolute bioavailability was estimated to be 6% (range, 1% to 19%). Plasma concentrations of alvimopan increased approximately proportionally with increasing doses between 6 and 18 mg, but less than proportionally from 18 to 24 mg.

There was a delay in the appearance of the 'metabolite', which had a median T_{max} of 36 hours following administration of a single dose of alvimopan. Concentrations of the 'metabolite' were highly variable between subjects and within a subject. The 'metabolite' accumulated after multiple doses of ENTEREG. The mean C_{max} for the 'metabolite' after alvimopan 12 mg twice daily for 5 days was 35.73±35.29 ng/mL.

Concentrations of alvimopan and its metabolite are higher (~1.9-fold and ~1.4-fold, respectively) in POI patients than in healthy volunteers.

Food Effects: A high-fat meal decreased the extent and rate of alvimopan absorption. The C_{max} and AUC were decreased by approximately 38% and 21%, respectively, and the T_{max} was prolonged by approximately 1 hour. The clinical significance of this decreased bioavailability is unknown. In POI clinical trials, the preoperative dose of ENTEREG was administered in a fasting state. Subsequent doses were given without regard to meals.

Distribution: The steady state volume of distribution of alvimopan was estimated to be 30±10 L. Plasma protein binding of alvimopan and its 'metabolite' was independent of concentration over ranges observed clinically and averaged 80% and 94%, respectively. Both alvimopan and the 'metabolite' were bound to albumin and not to alpha-1 acid glycoprotein.

Metabolism and Elimination: The average plasma clearance for alvimopan was 402 (±89) mL/min. Renal excretion accounted for approximately 35% of total clearance. There was no evidence that hepatic metabolism was a significant route for alvimopan elimination. Biliary secretion was considered the primary pathway for alvimopan elimination. Unabsorbed drug and unchanged alvimopan resulting from biliary excretion were then hydrolyzed to its 'metabolite'

by gut microflora. The 'metabolite' was eliminated in the feces and in the urine as unchanged 'metabolite', the glucuronide conjugate of the 'metabolite', and other minor metabolites. The mean terminal phase half-life of alvimopan after multiple oral doses of ENTEREG ranged from 10 to17 hours. The terminal half-life of the 'metabolite' ranged 10 to 18 hours.

Special Populations:

Age: The pharmacokinetics of alvimopan, but not its 'metabolite', were related to age, but this effect was not clinically significant and does not warrant dosage adjustment based on increased age.

Race: The pharmacokinetic characteristics of alvimopan were not affected by race. Plasma 'metabolite' concentrations were lower in black and in Hispanic patients (by 43% and 82%, respectively) than in Caucasian patients following alvimopan administration. These changes are not considered to be clinically significant in surgical patients; therefore, dosage adjustment based on race is not required.

Gender: There was no effect of gender on the pharmacokinetics of alvimopan or the 'metabolite'.

Hepatic Impairment: Exposure to alvimopan following a single 12-mg dose tended to be higher (1.5 to 2 fold, on average) in patients with mild or moderate hepatic impairment (as defined by Child-Pugh Class A and B, n = 8 each) compared with healthy controls (n = 4). There were no consistent effects on the C_{max} or half-life of alvimopan in patients with hepatic impairment. However, two of 16 patients with mild to moderate impairment had longer than expected half-lives of alvimopan indicating that some accumulation may occur upon multiple dosing. The C_{max} of the 'metabolite' tended to be more variable in patients with mild or moderate hepatic impairment than in matched normal subjects. A study of 3 patients with severe hepatic impairment (Child-Pugh Class C), indicated similar alvimopan exposure in 2 patients and an approximately 10-fold increase in C_{max} and exposure in 1 patient with severe hepatic impairment when compared with healthy control volunteers *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Renal Impairment: There was no relationship between renal function (i.e., creatinine clearance [CrCl]) and plasma alvimopan pharmacokinetics (C_{max}, AUC, or half-life) in patients with mild (CrCl 51-80 mL/min), moderate (CrCl 31-50 mL/min), or severe (CrCl <30 mL/min) renal impairment (n = 6 each). Renal clearance of alvimopan was related to renal function; however, because renal clearance was only a small fraction (35%) of the total clearance, renal impairment had a small effect on the apparent oral clearance of alvimopan. The half-lives of alvimopan were comparable in the mild, moderate and control renal impairment groups but longer in the severe renal impairment group. Exposure to the 'metabolite' tended to be 2- to 5-fold higher in patients with moderate or severe renal impairment compared to patients with mild renal impairment or control subjects. Thus, there may be accumulation of alvimopan and 'metabolite' in patients with severe renal impairment receiving multiple doses of ENTEREG. Patients with end-stage renal disease were not studied *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.6)]*.

Crohn's Disease: There was no relationship between disease activity in patients with Crohn's disease (measured as Crohn's Disease Activity Index or bowel movement frequency) and alvimopan pharmacokinetics (AUC or C_{max}). Patients with active or quiescent Crohn's disease had increased variability in alvimopan pharmacokinetics and exposure tended to be 2-fold higher in patients with quiescent disease than in those with active disease or normal subjects. Concentrations of the 'metabolite' were lower in patients with Crohn's disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two year carcinogenicity studies have been conducted with alvimopan in CD-1 mice at oral doses up to 4000 mg/kg/day and in Sprague Dawley rats at oral doses up to 500 mg/kg/day. Oral administration of alvimopan for 104 weeks produced significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice at 4000 mg/kg/day (about 674 times the recommended human dose based on body surface area). In rats, oral administration of alvimopan for 104 weeks did not produce any tumor up to 500 mg/kg/day (about 166 times the recommended human dose based on body surface area).

Alvimopan was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/$TK^{+/-}$) forward mutation test, the Chinese Hamster Ovary (CHO) cell chromosome aberration test or the mouse micronucleus test. The pharmacologically active 'metabolite' ADL 08-0011 was negative in the Ames test, chromosome aberration test in CHO cells and mouse micronucleus test.

Alvimopan at intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single oral dose of 500 mg/kg of alvimopan was not lethal to mice and rats.

Reproduction studies have been performed in pregnant rats at oral doses up to 200 mg/kg/day (about 68 to 136 times the recommended human oral dose based on the body surface area) and intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at intravenous doses up to 15 mg/kg/day (about 5 to 10 times the recommended human oral dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan.

14 CLINICAL STUDIES

14.1 Postoperative Ileus

The efficacy of ENTEREG in the management of postoperative ileus was evaluated in 5 multicenter, randomized, double-blind, parallel-group, placebo-controlled studies: 4 US studies (Studies 1-4) and 1 non-US study (Study 5). Patients 18 years of age or older undergoing partial large or small bowel resection surgery with primary anastomosis or total abdominal hysterectomy under general anesthesia were randomly assigned to receive oral doses of ENTEREG 12 mg or matching placebo. The initial dose was administered at least 30 minutes

and up to 5 hours prior to the scheduled start of surgery for most patients, and subsequent doses were administered twice daily beginning on the first postoperative day and continued until hospital discharge or a maximum of 7 days. There were no limitations on the type of general anesthesia used, but intrathecal or epidural opioids or anesthetics were prohibited.

All patients in the US studies were scheduled to receive intravenous patient-controlled opioid analgesia. In the non-US study, patients were scheduled to receive opioids either by intravenous patient-controlled opioid analgesia or bolus parenteral administration (intravenous or intramuscular). In all studies, there was no restriction on the type of opioid used or the duration of intravenous patient-controlled opioid analgesia. A standardized accelerated postoperative care pathway was implemented: early nasogastric tube removal (end of surgery); early ambulation (day following surgery); early diet advancement (liquids offered the day following surgery) and solids by the second day following surgery, as tolerated.

Patients who received more than 3 doses of an opioid (regardless of route) during the 7 days prior to surgery and patients with complete bowel obstruction or who were scheduled for a total colectomy, colostomy, or ileostomy were excluded.

The primary endpoint for all studies was time to achieve resolution of postoperative ileus, a clinically defined composite measure of both upper and lower gastrointestinal recovery. Although both 2-component (GI2: toleration of solid food and first bowel movement) and 3-component (GI3: toleration of solid food and either first flatus or bowel movement) endpoints were used in all studies, GI2 is presented as it represents the most objective and clinically relevant measure of treatment response in the bowel resection population. The time from the end of surgery to when the discharge order was written represented the length of hospital stay. In the 5 studies, 1,081 patients received placebo (157 for total abdominal hysterectomy) and 1,096 patients received ENTEREG (143 for total abdominal hysterectomy).

The efficacy of ENTEREG following total abdominal hysterectomy has not been established. Therefore, the following data are presented for the bowel resection population only.

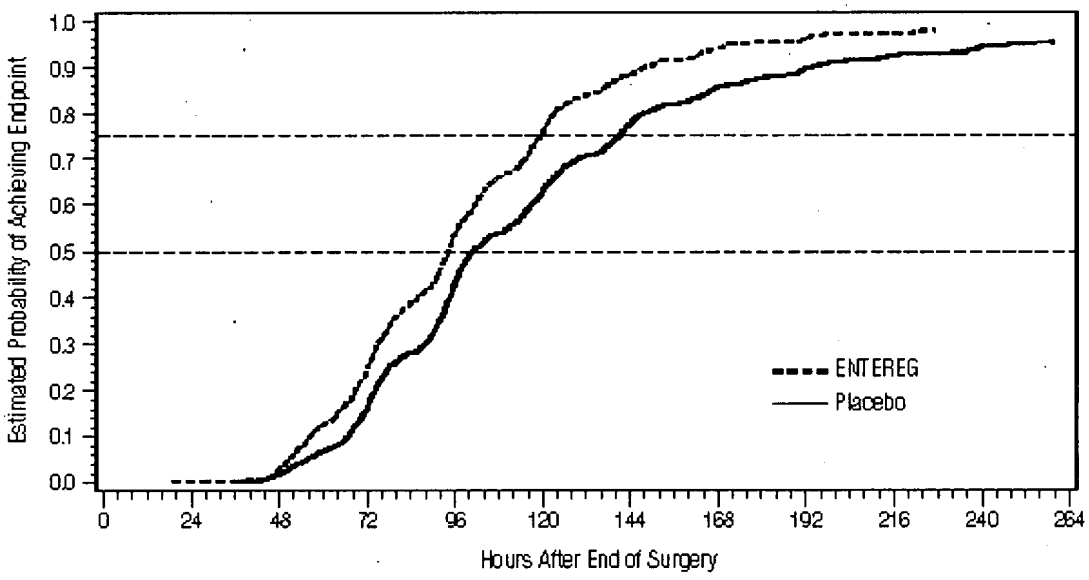
Bowel Resection: A total of 1,877 patients underwent bowel resection. The average age was 61 years with equal proportions of males and females, and 88% were Caucasian. The most common indications for surgery were colon or rectal cancer and diverticular disease. In the non-US study (Study 5), average daily postoperative opioid consumption was approximately 50% lower and the use of non-opioid analgesics substantially higher, as compared with the US studies (Studies 1-4) for both treatment groups. During the first 48 hours postoperatively, the use of non-opioid analgesics was 69% compared with 4% for the non-US and US studies, respectively. In each of the 5 studies, ENTEREG accelerated the time to recovery of gastrointestinal function, as measured by the composite endpoint GI2, and time to discharge order written as compared with placebo. Hazard ratios greater than 1 indicate a higher probability of achieving the event during the study period with treatment with ENTEREG than with placebo. Table 2 provides the Hazard Ratios, Kaplan Meier means and the mean treatment differences (hours) in gastrointestinal recovery between ENTEREG and placebo.

Table 2. GI2 Recovery (Hours) in Bowel Resection Patients

Study No.	ENTEREG 12 mg Mean	Placebo Mean	Treatment Difference Mean	Hazard Ratio (95% CI)
1	92.0	111.8	19.8	1.533 (1.293, 1.816)
2	105.9	132.0	26.1	1.625 (1.256, 2.102)
3	116.4	130.3	14.0	1.365 (1.057, 1.764)
4	106.7	119.9	13.2	1.400 (1.035, 1.894)
5	98.8	109.5	10.7	1.299 (1.070, 1.575)

Gastrointestinal recovery began after approximately 48 hours post surgery. The proportion of patients receiving ENTEREG who achieved GI2 was higher at all times throughout the study observation period compared with those receiving placebo (Figure 1).

Figure 1 Time to GI2 Based on the Combined Data from Five Studies



Across studies 1-4, patients receiving ENTEREG had their discharge order written approximately 13 to 21 hours sooner compared to patients receiving placebo.

ENTEREG did not reverse opioid analgesia as measured by visual analog scale pain

intensity scores and/or amount of postoperative opioids administered across all 5 studies.

There were no gender-, age-, or race-related differences in treatment effect.

The incidence of anastomotic leak was low and comparable in patients receiving either ENTEREG or placebo (0.8% and 1.1%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTEREG Capsules, 12 mg, are blue, hard-gelatin capsules printed with "ADL2698" on both the body and the cap of the capsule. ENTEREG Capsules are available in unit-dose packs of 30 capsules (30 doses) (NDC 11227-010-30) for hospital use only.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

17.1 Recent Use of Opioids

Patients should be informed that they must disclose long-term or intermittent opioid pain therapy, including any use of opioids in the week prior to receiving ENTEREG. They should understand that recent use of opioids may make them more susceptible to adverse reactions to ENTEREG, primarily those limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea).

17.2 Hospital Use Only

Patients should be informed that ENTEREG is for hospital use only for no more than 7 days after their bowel resection surgery.

17.3 Most Common Side Effects

Patients should be informed that the most common side effects with ENTEREG in patients undergoing bowel resection are constipation, dyspepsia, and flatulence.

adolor CORPORATION

Manufactured for Adolor Corporation
Exton, PA 19341-1127

gsk GlaxoSmithKline

Distributed by GlaxoSmithKline
Research Triangle Park, NC 27709

US Patent Nos. 5,250,542; 5,434,171; 6,469,030

EXHIBIT 3

US005434171A

United States Patent [19]

Frank et al.

[11] Patent Number: 5,434,171

[45] Date of Patent: Jul. 18, 1995

[54] **PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYLCARBOXYLATES AND INTERMEDIATES**

[75] Inventors: **Scott A. Frank**, Lebanon; **Douglas E. Prather**, Brownsburg; **Jeffrey A. Ward**; **John A. Werner**, both of Indianapolis, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **164,074**

[22] Filed: **Dec. 8, 1993**

[51] **Int. Cl.**[6] **A61K 31/445**; C07D 211/32

[52] **U.S. Cl.** **514/331**; 514/317; 546/236; 546/237; 546/238; 546/239; 546/240

[58] **Field of Search** 546/236, 237, 238, 239, 546/240; 514/317, 331

[56] **References Cited**

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Primary Examiner—Ceila Chang

Attorney, Agent, or Firm—MaCharri Vorndran-Jones

[57] **ABSTRACT**

This invention relates to a process for preparing certain 3,4,4-trisubstituted-piperidinyl-N-alkylcarboxylates, intermediates, and congeners. Finally, the invention provides new 3,4,4-trisubstituted-piperidinyl-N-alkylcarboxylates with formulations and methods for using the compounds.

17 Claims, No Drawings

PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYL-CARBOXYLATES AND INTERMEDIATES

FIELD OF THE INVNETION

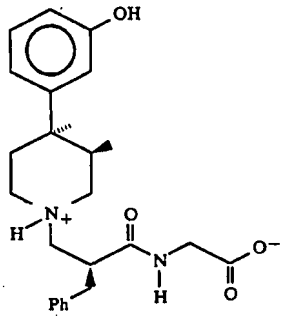
This invention relates to a process for preparing certain 3,4,4-trisubstituted-piperidinyl-N-alkylcarboxylates, new intermediates and their congeners. Finally, this invention provides stable crystalline compounds and formulations useful as peripheral opioid antagonists.

BACKGROUND OF THE INVENTION

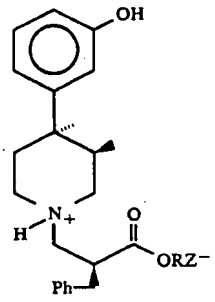
A substantial body of evidence indicates that peripheral opioid peptides and their receptors have a major physiological role in the regulation of gut motility. Consequently, gastrointestinal disorders such as idiopathic constipation and irritable bowel syndrome may relate to a dysfunction of opioid receptor mediated control, and agents which act as antagonists for these receptors may benefit a patient suffering from such a dysfunction.

The N-substituted piperidines, prepared using the process and intermediates of this invention are useful as peripherally-selective opioid antagonists. One particularly desirable 3,4,4-trisubstituted-piperidinyl-N-alkylcarboxylate is (2S,3R,4R)([[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid (1).

(1)



(2)



A generic process to prepare (αS,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidine propanoic acid ethyl ester (2), a useful intermediate for the preparation of 1, is known to the skilled artisan. Zimmerman describes this process in U.S. Pat. No. 5,250,542 (hereincorporated by reference). However, this process produces a mixture of stereoisomeric products which prevents its utilization in a practical commercial process. The preparation of the desired compound of Formula 1 requires a tedious chromatographic separation with only 13% yield for the isomer separation. Further, each intermediate is isolated as a "gum-like" product due to the presence of the undesired isomer. The "gum-like" product precludes purification of any intermediate without chromatography and is highly undesirable for commercial purposes.

The process of this invention now provides a synthetic route which will provide crystalline intermediates, without epimerization to facilitate the commercial preparation of 1 and C_1–C_6 alkyl esters thereof. Additionally, the process of this invention produces a crystalline solid of 1 and C_1–C_6 alkyl esters thereof in acceptable yields. Finally, the synthetic process of this invention includes crystalline intermediates to provide both enrichment and purification of the desired product.

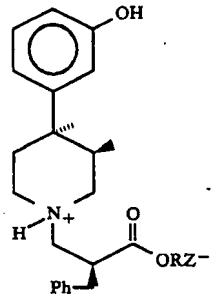
This invention provides a highly desirable stable crystalline (2S,3R,4R)([[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1 -piperidinyl]methyl]-1-oxo-3-phenylpropyl-]amino]acetic acid (1) which is the dihydrate.

The new crystalline intermediates and crystallization method are particularly important for the commercial development of the pharmaceutically active 3-4,4-trisubstituted-piperidinyl-N-alkylcarboxylates (18 and 18*a* infra.).

SUMMARY OF THE INVENTION

The presently claimed invention provides new crystalline salts of the Formula 2

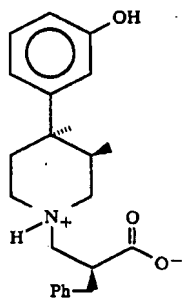
(2)



wherein R is C_1–C_6 alkyl; $z^-$is selected from the group consisting of chloride, bromide, succinate, and (+)—dibenzoyltartrate; in acceptable yields.

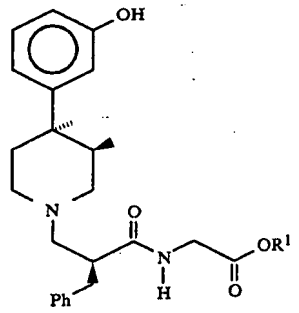
The invention provides a process for preparing a crystalline monohydrate compound of Formula 3

(3)



comprising the crystallization of 3 from a solvent comprised of about 50% to 75% lower alcohol and about 50% to 25% water (by weight).

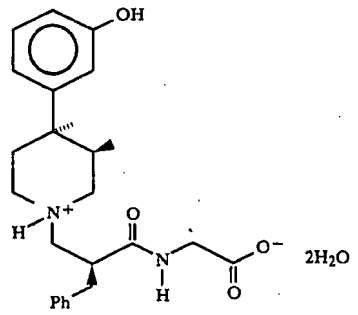
Further, this invention provides crystalline compounds of the Formula 4



(4)

wherein R^1 is C_1–C_6 alkyl; the compound is a salt selected from the group consisting of hydrochloride and L-malate. The hydrochloride salt is a unique crystal form existing as the acetone monosolvate. The L-malate salts are also unique because their stoichiometry is dependent upon the solvent of crystallization. The stoichiometry may be either 1 molar equivalent each of L-malic acid and a compound of 4 or may be 3 molar equivalents of L-malic acid and 2 molar equivalents of a compound of 4. As used herein, the term "sesquimalate" refers to a 3:2 ratio of L-malic acid to compound 4.

Finally, this invention provides a crystalline dihydrate compound of the Formula 5



(5)

DETAILED DESCRIPTION OF THE INVENTION

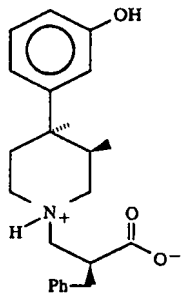
The term "C_1–C_6 alkyl", as used herein, represents a branched or linear alkyl group having from one to six carbon atoms. Typical C_1–C_6 alkyl groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, and the like. Other such terms represent straight chain or branched alkyl groups of the specified number of carbon atoms. For example, "C_1–C_3 alkyl" represents methyl, ethyl, n-propyl, and isopropyl.

The term "lower alcohol" refers to methanol, ethanol, 1-propanol, and 2-propanol.

The terms "inert atmosphere" and "inert conditions" refer to reaction conditions in which the mixture is covered with a layer of inert gas such as nitrogen or argon.

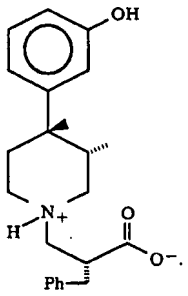
The term "substantially pure" is used herein to refer to at least about 90 mole percent of the desired absolute stereoisomer and/or polymorph. More preferably at least about 95 mole percent and most preferably at least about 98 mole percent of the desired absolute stereoisomer and/or polymorph is present.

Most preferably, the product of the process and compounds of the present invention are compounds existing as the 3R,4R-isomer as shown in Formula 3



(3)

or the 3S,4S-isomer of Formula 6



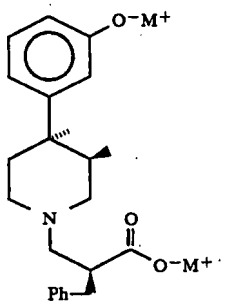
(6)

Further, the artisan will recognize that the benzyl substituent attaches at a chiral center. This invention encompasses both the (αS,3R,4R) and (αR,3S,4S) diastereomers. Especially preferred compounds of the present invention are those of Formulas 2, 3, 4, and 5 in which the configuration of substituents on the piperidine ring is 3R, 4R, and the carbon bearing the benzyl group is S. The artisan can choose appropriate reagents to prepare the opposite enantiomer.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote the specific configuration of a chiral center. See, Organic Chemistry, R.T.Morrison and R.N. Boyd, 4th ed., Allyn & Bacon, Inc., Boston (1983), pp 138–139 and *The Vocabulary of OrGanic Chemistry*, Orchin, et al., John Wiley and Sons Inc., p 126.

The term "hydrolysis" as used herein includes all appropriate known ester hydrolysis methods, including acidic, basic, and enzymatic processes. Preferred methods are described infra.

As used herein, the phrase "the crystallization of 3" refers to neutralizing the product of the hydrolysis reaction; Formula 7



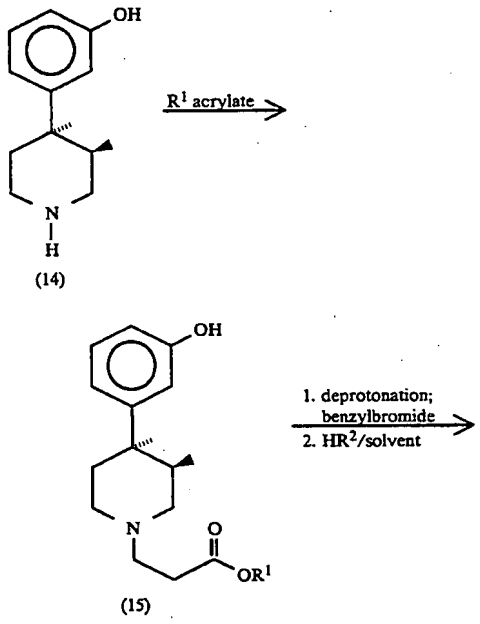
(7)

wherein M+is sodium, lithium, or potassium, with the designated reagents and/or solvents and crystallizing using known techniques. The mixing may be accomplished using common agitation methods such as stirring, shaking, and the like. Further, the artisan recognizes that crystallization processes may include seeding, chilling, scratching the glass of the reaction vessel, and other such common techniques.

The starting materials for the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The 3-substituted-4-methyl-4-(3-hydroxy- or alkanoyloxyphenyl)piperidine derivatives employed as starting materials in the process of this invention can be prepared by the general procedure taught by Zimmerman in U.S. Pat. No. 4,115,400 (1978) and Zimmerman et al. in U.S. Pat. No. 4,891,379 (1990). U.S. Pat. Nos. 4,115,400 and 4,891,379 are incorporated herein by reference. The starting material for the synthesis of the compounds of the present invention, (3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidine, can be prepared by the procedure of Zimmerman in U.S. Pat. No. 5,250,542, herein incorporated by reference. The artisan should particularly note Example 1 of Zimmerman '542.

The starting material, 14, prepared as described in the art, can be used in the process of Scheme 1 (infra).

Scheme 1

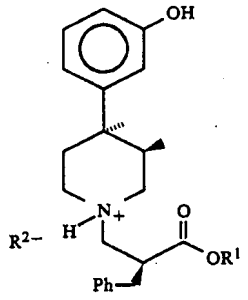


(14)

(15)

-continued

Scheme 1



(16)

Wherein R^1 is defined supra. R^2 is chloride, bromide, (+)-dibenzoyltartrate, or succinate.

As illustrated in Scheme 1, compound 14 is contacted with an alkyl acrylate (R^1 acrylate) to form 15. R^1 is defined supra. Suitable solvents include methanol, tetrahydrofuran, ethanol, and others. The most preferred solvents are methanol and tetrahydrofuran.

Compound 15 is deprotonated and contacted with benzyl bromide. The deprotonation may be accomplished using an appropriate base. Examples of suitable base reagents include lithium diisopropylamide or lithium hexamethyldisilazide. Preferred solvents for the base reaction include tetrahydrofuran and 1,2-dimethoxyethane. The artisan will recognize that other solvents may be appropriate. When lithium diisopropylamide (LDA) is the base, it is most preferred that 2 equivalents of benzyl bromide are present. The alkylation product is a 1:1 mixture of the (αS, 3R, 4R)-isomer and the (αR, 3R, 4R)-isomer.

Crystalline compounds of formula 16 are new and unique. Only four specific salts of 16 were both stable crystalline salts and provided the desired diastereomeric enrichment. The following acids were each studied using four different solvent systems: HCl, HBr, (+)-dibenzoyl tartaric, succinic, (−)-di-p-toluoyl tartaric, (+)-di-p-toluoyl tartaric, (−)-dibenzoyl tartaric, (1R,3S)-(+)-camphoric, hippuric, benzoic, L-malic, D-malic, malonic, D-aspartic, (−)-tartaric, (+)-tartaric, (−)-mandelic, (+)-mandelic, L-ascorbic, maleic, sulfuric, acetic, phosphoric, citric, lactic, p-toluenesulfonic, D-arabascoric, and L-aspartic. Thus, over 110 crystallization studies yielded only four stable crystalline salts which provide enrichment! The enrichment and yield of the four stable crystalline salts is illustrated in Table I.

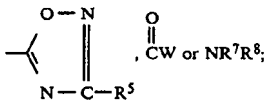
TABLE I

Crystalline salts of the ester.			
Salt	Diast. Ratio	Yield	Solvent of Crystallization
hydrochloride	88/12	39%	methanol
hydrobromide	79/21	42%	methanol
(+)-DBTA[a]	71/29	25%	ethyl acetate:acetone (1:1)
succinate	83/17	25%	ethyl acetate:acetone (1:1)

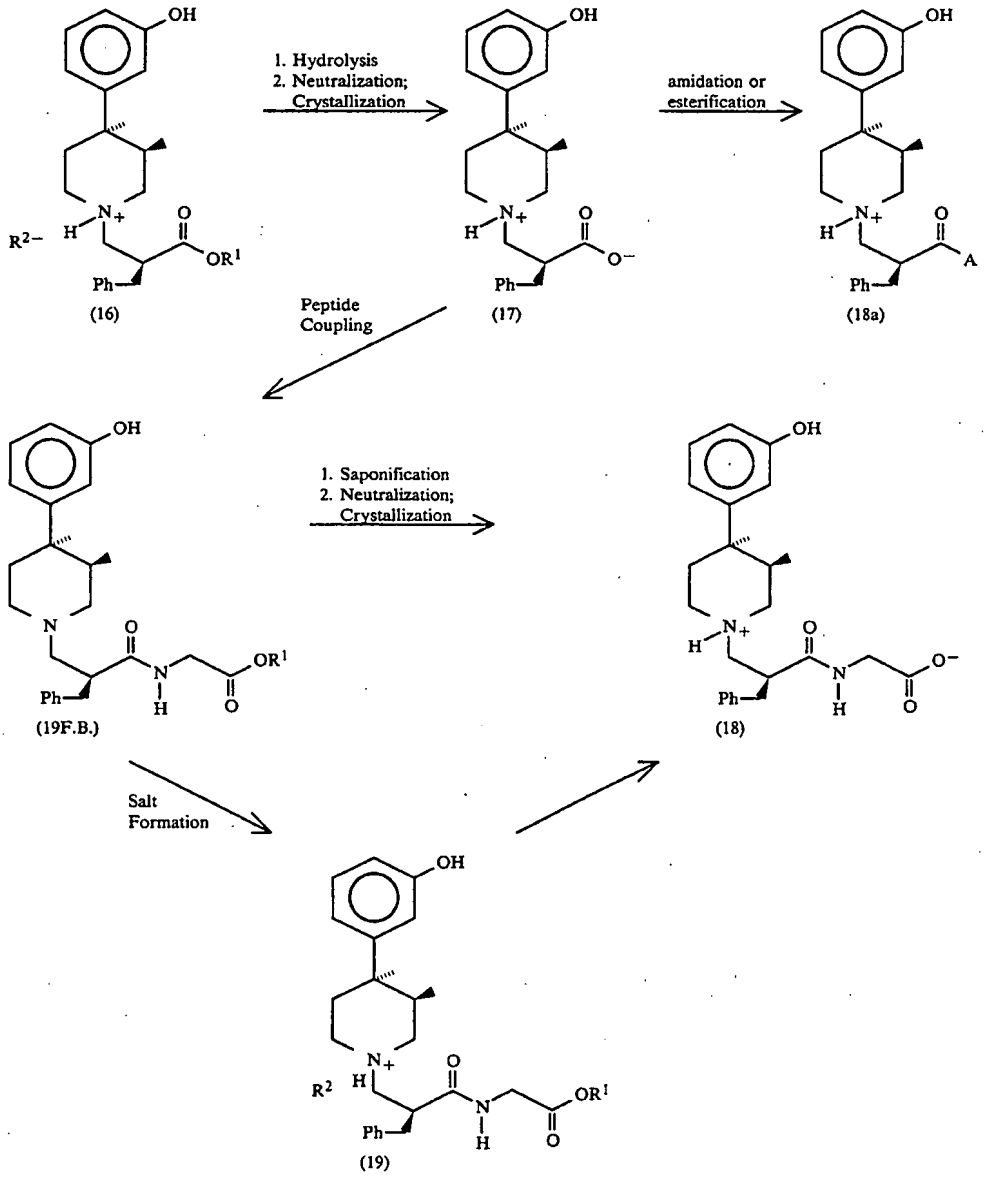
[a] (+)-dibenzoyl tartrate

As illustrated by Scheme 2 (infra), compound 16 is subject to hydrolysis to form compound 17. The artisan will recognize that compound 17 will be useful for preparing other useful compounds as illustrated by compound 18*a*. Compounds 18*a* are generically disclosed in U.S. Pat. No. 5,250,542 as being useful opioid antago-

nists. For the first time it is possible to prepare the pure absolute stereochemical isomers (18 and 18*a*) without tedious chromatographic separations using the new intermediates of this invention.



Scheme 2



wherein R^1 and R^2 are as defined supra.

A is OR^4 or NR^5R^6; wherein:

R^4 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

R^5 is hydrogen or C_1–C_3 alkyl;

R^6 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl, phenyl cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl, or (CH_2) q-B; or

R^5 and R^6 together with N form a saturated non aromatic 4 to 6-membered heterocyclic ring;

R^7 iS hydrogen or C_1–C_3 alkyl;

R^8 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl or phenyl-substituted C_1–C_3 alkyl; or

R^7 and R^8 together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

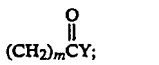
w is OR^9, $NR^{10}R^{11}$, or OE;

R^9 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted

C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

R^{10} is hydrogen or C_1–C_3 alkyl;

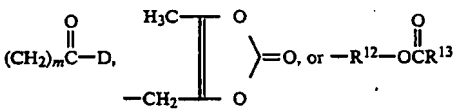
R^{11} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl, or



or

R^{10} and R^{11} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

E is



R^{12} is C_1–C_3 alkyl substituted methylene,

R^{13} is C_1–C_{10} alkyl;

D is OR^{14} or $NR^{15}R^{16}$; wherein:

R^{14} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

R^{15} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, phenyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl; and

R^{16} is hydrogen or C_1–C_3 alkyl; or

R^{15} and R^{16} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

Y is OR^{17} or $NR^{18}R^{19}$;

R^{17} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cyclocalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl;

R^{18} is hydrogen or C_1–C_3 alkyl; and

R^{19} is is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl; or

R^{18} and R^{19} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

q is 1–4;

m is 1–4.

The "A" substituent is described in U.S. Pat. No. 5,250,542.

The hydrolysis reaction may be completed using known acidic hydrolysis methods. An example of one such acidic hydrolysis method is treatment with an aqueous acid in refluxing dioxane. More preferredly, the hydrolysis reaction is completed using saponification conditions to avoid epimerization. Examples of saponification reagents include lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like.

The product of the hydrolysis reaction (the carboxylate salt) is adjusted to the isoelectric point of the amino acid using aqueous acid to provide the zwitterion 17. Crystallization of the monohydrate of 17 must be completed using 50% to 75% lower alcohol and 50% to 25% water.

Table I illustrates the critical dependence of the crystallization on the approximate 1:1 lower alcohol/water solvent. The term "gumball" refers to the coagulation of a sticky semi-solid product into an amorphous mass.

TABLE I

Entry	% cosolvent	Acid Conc.	Yield	Comments
1	none	12N HCl	86%	gumball
2	none	12N HCl	88%	gumball
3	none	12N HCl	93%	gumball
4	none	1N HCl	90%	gumball
5	none	6N HCl	91%	gumball
6	none	1M H_3PO_4	93%	gumball
7	none	6M H_3PO_4	97%	gumball
8	none	1M AcOH	99%	gumball
9	6 MeOH	12N HCl	88%	gumball
10	12 MeOH	12N HCl	87%	gumball
11	25 MeOH	12N HCl	82%	gumball
12	25 MeOH	12N HCl	90%	gumball
13	50 MeOH	12N HCl	58%*	gumball
14	50 MeOH	12N HCl	82%	crystal
15	50 MeOH	12N HCl	90%**	crystal
16	50 MeOH	12N HCl	95.9%**	crystal
17	50 i-Pr	12N HCl	73%	crystal
18	50 ACN	12N HCl	23%	crystal

ACN refers to acetonitrile; i-Pr refers to isopropyl alcohol.* Due to reaction concentration of 10mL solvent/g of 16 ** Yield increase is due to removal of methanol by distillation after crystallization has occurred.

As illustrated in Scheme 2, the product 17 can be used directly in the amidation/esterification step. When amidation is desired, the amino acid should be selected to produce the desired compounds of formula 18 or 18*a*. The amino acid is contacted with a glycine ester in a solvent such as dimethylformamide or tetrahydrofuran. Dicyclohexylcarbodiimide is used as the coupling reagent. N-hydroxybenzotriazole is added as the auxiliary nucleophile. The coupling reaction may be run under inert conditions. More preferably, the peptide coupling reaction uses tetrahydrofuran as the solvent. The artisan will recognize that other peptide coupling methods will also be effective.

Alternatively, a crystalline salt of compound 19F.B. (free base) can be prepared as illustrated in Scheme 2 supra. Crystallization studies were conducted using 17 different acids with three solvents; ethyl acetate, acetone, and ethanol. Of those 51 experiments, only the L-malic and hydrochloric acids yielded crystalline salts stable at 25 ° C.

The crystalline hydrochloride salt is obtained by contacting 19F.B. with anhydrous HCl in acetone. Capillary gas chromatographic analysis indicates that the salt is produced as the monosolvate of acetone. This unique monosolvate crystal form allows compound 19 to be isolated in substantially pure form. Contacting 19F.B. with anhydrous HCl in other solvents produces an amorphous solid without substantial purification.

Applicants have discovered that the L-malic acid salt can be prepared as a stable crystalline solid having two ratios of 19F.B. to L-malic acid, depending on the solvent of crystallization. When the crystallization is completed in solvents such as methyl ethyl ketone, acetone, acetone/t-butyl methyl ether, or acetone/heptane the expected stoichiometry of 1:1 19F.B. to L-malic acid is found. However, when the crystallization is carried out in solvent systems of acetone/ethyl acetate, acetone/-toluene, or ethanol/toluene the crystalline salt is afforded with the unique stoichiometry of a 3:2 ratio of L-malic acid to 19F.B.(sesquimalate) This result is par-

ticularly unexpected when the sesquimalate is obtained even when a 1:1 ratio of malic acid and 19F.B. are combined in certain solvents. Indeed, when equimole amounts of L-malic acid and 19F.B. are combined in a sesquimalate-forming solvent or solvent system, the sesquimalate is the sole salt formed in about 67% yield, with the mass balance being 19F.B. in the mother liquor. Certainly, the artisan would expect the ratio to be 1:1. Moreover, crystallization of a sesquimalate salt in a "non-sesquimalate-forming" solvent of solvent systems forms only the crystalline monomalate salt in nearly quantitative yield, with the excess L-malic acid remaining in the mother liquor.

Crystallization of the sesquimalate salt provides a product of pharmaceutically acceptable purity in a high yield with crystals of highly consistent crystal form and size. The hydrochloride and sesquimalate salts can be used as prodrug entities since the isobutyl ester is readily cleaved in vivo.

The acids which did not form crystalline salts stable at 25° C. include HBr, H_2SO_4, hippuric, d-tartaric, l-tartaric, malonic, succinic, acetic, arabascorbic, ascorbic, citric, benzoic, lactic, (S)-(+)-mandelic, and (R)-(−)-mandelic acids. Thus, demonstrating the surprising and unique nature of the L-malic and HCl salts.

The product of the amidation/esterification reaction or salt forms thereof, can be hydrolyzed using standard methods. Preferably, basic hydrolysis methods are used. Preferred saponification reagents include sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like. Most preferably, the saponification step is completed using sodium hydroxide and a solvent. Particularly preferred solvents are (1:1) methanol:water and (2:1) ethanol:water. The reaction is quenched using an acid such as hydrochloric acid. After neutralization (pH=6), the crystalline solid dihydrate product 18 is directly isolated by filtration. The isolated product 18 is of pharmaceutically acceptable purity without subsequent purification steps.

The new dihydrate 18 is particularly desirable because the compound is a stable crystalline solid, is of consistent crystal form and particle size to provide reproducible dissolution rates, and is of pharmaceutically desirable quality.

The compounds of Formula 5 and 4 supra. are useful in blocking peripheral opioid receptors and preventing peripheral opiate induced side effects. These side effects are induced by administration of an opiate such as morphine to a mammal. The opiate induced side effects can include constipation, nausea, and vomiting. Thus, the compounds of this invention are useful for treating one or more opiate induced side effects. These compounds can also be useful in the treatment of irritable bowel syndrome, non-ulcer dyspepsia, and idiopathic constipation. These compounds do not substantially pass through the blood-brain barrier and therefore do not mitigate the opioid's effect on central (brain and spinal cord) opioid receptors. Consequently, these characteristics indicate that the compounds will also be substantially free of other centrally mediated effects.

In order to determine in vivo opioid receptor antagonism, the mouse writhing analgesis test was used. Test compounds were measured for their ability to block morphineinduced analgesia.

Five CF-1 male mice (Charles River, Portage, MI), weighing approximately 20 g after being fasted overnight, were observed simultaneously for the writhing response. The writhing response was defined as a contraction of the abdominal musculature, followed by the extension of the hind limbs, and was induced by the intraperitoneal administration of 0.6% acetic acid in a volume of 1 mL/100 g of body weight. The observation period was 10 minutes in duration, beginning 5 minutes after injection of acetic acid. The percent inhibition of writhing was calculated from the average number of writhes in the control (non-drug) group. The ED_{50} was defined as the dose of agonist that inhibited mean writhing by 50%. The AD_{50} was defined as the dose of antagonist that reduced the inhibition of writhing produced by a 1.25 mg/kg dose of morphine sulfate to 50%. Each mouse was used only once. All drugs were administered subcutaneously (1 mL/100 g bwt) 20 minutes before the injection of acetic acid.

Determinations of peripheral opioid activity were conducted. Mice were maintained on 0.01 M. saccharin water with 1 g/L morphine sulfate for a minimum of 10 days with the mice averaging over 3.0 g of water per mouse per day for at least 3 days. The morphine water was removed 45 minutes prior to injection with the proposed opioid antagonist. After administration of the opioid antagonist, the mice were placed in plastic cylinders with white paper towels for a floor.

The mice were monitored visually for 30 minutes post-injection for the presence of jumping and of diarrhea. Jumping was scored as positive if at least one jump occurred in 30 minutes. Diarrhea was scored as positive when feces were moist enough to stain the white paper at the base of the cylinder. After 30 minutes of testing, the mice were returned to their original cages, put back on morphine water, and not tested again for 48 hours. Lower doses of the antagonist compounds were tested until threshold doses for diarrhea were determined. Diarrhea is a peripherally mediated sign of precipitated opiate abstinence.

The extent of the effect on peripheral activity compared to central activity of the present compounds can be determined by comparing the AD_{50} for the mouse writhing test with the ED_{50} for the mouse diarrhea test. The higher the ratio, the greater relative antagonism of the peripheral opioid receptors by a particular compound.

The AD_{50} values for the compounds of this invention are over 8 mg/kg, while the ED_{50} values are under 1.

Further, the compounds of Formulas 5 and 4 supra. have been found to display excellent activity in an opioid receptor binding assay which measures the affinity of the compounds to bind mu receptors. This assay was conducted by the following procedure.

Male Sprague Dawley rats were sacrificed via decapitation and the brains were removed. The brain tissue with the cerebellum removed was homogenized in a Teflon and glass tissue homogenizer. A supernatant I, pellet IV, fraction was frozen in a nitrogen freezer at 1.33 g/mL concentration and stored for not longer than five weeks prior to use.

increasing concentrations of experimental compound, (0.1 to 1000 nanomolar (nM)), Krebs-Hepes buffer pH 7.4, and tritiated naloxone (0.5 nM) (^3H ligand) were combined in polystyrene tubes at room temperature. The reaction was initiated by the addition of the resuspended tissue which had been preincubated at 37° C. for 20 minutes. The reaction mixture was incubated in a 37° C. water bath for 20 minutes. The reaction was terminated by rapid filtration, (Brandel cell harvester), through Whatman GF/B glass filters that had been presoaked in Krebs-Hepes buffer pH 7.4. The filters

were then washed 2 times with 5 mL of ice cold Krebs-Hepes buffer of pH 7.4. Washed filters were placed in scintillation vials and 10 mL, (Brandel), was added and samples were counted in a Searle D-300 beta counter. The incubation time for the reaction mixture was 20 minutes at 37° C. The K_i and K_D values were calculated using standard methods.

The compounds of this invention exhibit highly desirable activity profiles. The value for percent displacement by the test compounds at 10 nM concentration was over 75% and over 80% at 100 nM. This is particularly desirable in light of the AD_{50} and ED_{50} values (supra). The results indicate that the compounds of this invention have favorable activity profiles for use in the treatment of irritable bowel syndrome and conditions related to the binding of mu receptors.

While it is possible to administer a compound of this invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the invention. The effective dosage range for the compounds of this invention is broad. Thus, such compositions contain from about 0.1 percent by weight to about 90.0 percent by weight of a presently claimed compound. As such, the present invention also provides pharmaceutical formulations comprising a compound of this invention and a pharmaceutically acceptable excipient therefor.

In making the formulations of the present of the present invention, the acnive ingredient is usually mixed with an excipient which can be a carrier, or a diluent, or be diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it can be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the formulation can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), suppository, and soft and hard gelatin capsules.

The compounds of this invention may be delivered transdermally, if desired. Transdermal permeation enhancers and delivery systems, including patches and the like are well known to the skilled artisan.

Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compounds of this invention may be delivered transdermally using known transdermal delivery systems and excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not limited to, propylene glycol, polyethylene glycol, monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules. The compounds of this invention may be prepared as microparticles or microspheres. Microparticles may be prepared using polyglycolide, polylactide, or other polymers to facilitate sustained release of the active compound or prodrug.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. Another preferred range is about 0.5 mg to about 60 mg of the active ingredient per unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical carrier.

The artisan will recognize that the compounds of this invention may be formulated with other known medicaments. The co-formulation may provide a synergistic therapeutic effect. For example, an antacid can be formulated with the compounds of this invention to provide a desired gastrointestinal effect.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

FORMULATION 1

Hard gelatin capsules are prepared using the following ingredients:

	Amount Per Capsule	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid methyl ester, hydrochloride	250 mg	55.0
Starch dried	200 mg	43.0
Magnesium stearate	10 mg	2.0
	460 mg	100.0

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Capsules each containing 20 mg of medicament are made as follows:

	Amount Per Capsule	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenylpropyl]amino]acetic acid ethyl ester, hydrochloride monohydrate	20 mg	10

-continued

	Amount Per Capsule	Concentration by Weight (percent)
Starch	89 mg	44.5
Microcrystalline cellulose	89 mg	44.5
Magnesium stearate	2 mg	1.0
	200 mg	100.0

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

Formulation 3

Capsules each containing 100 mg of medicament are made as follows:

	Amount Per Capsule	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenyl-propyl]amino]acetic acid, dihydrate	100 mg	30.0
polyoxyethylene sorbitan monooleate	50 mg	0.02
starch powder	250 mg	69.98
	350 mg	100.0

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

Formulation 4

Tablets containing 10 mg of active ingredient are made as follows:

	Amount Per Tablet	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl] methyl]-1-oxo-3-phenyl-propyl]amino]acetic acid, ethyl ester, sesquimalate	10 mg	10.0
Starch	45 mg	45.0
Microcrystalline Cellulose	35 mg	35.0
Polyvinylpyrrolidone (as 10% solution in water)	4 mg	4.0
Sodium Carboxymethyl Starch	4.5 mg	4.5
Magnesium Stearate	0.5 mg	0.5
Talc	1 mg	1.0
	100 mg	100.0

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°–60° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

Formulation 5

A tablet formulation may be prepared using the ingredients below:

	Amount Per Tablet	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenyl-propyl]amino]acetic acid, dihydrate	250 mg	38.0
Microcrystalline cellulose	400 mg	60.0
Silicon Dioxide fumed	10 mg	1.5
Stearic Acid	5 mg	0.5
	665 mg	100.0

The components are blended and compressed to form tablets weighing 665 mg.

Formulation 6

A hard gelatin capsule may be prepared using the following ingredients:

	Amount Per Capsule	Concentration by Weight (percent)
(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenyl-propyl]amino]acetic acid, dihydrate	66 mg	18
Polyethylene Glycol	300 mg	82
	366 mg	100

All solid ingredients are sieved. Polyethylene Glycol is melted and maintained in a molten state. The medicament is incorporated into the molten vehicle. The molten homogeneous suspension is filled into hard gelatin capsules to the appropriate weight or volume using suitable oil paste filling equipment.

Capsules containing 6 mg of active substance may be prepared exactly as describe above; however, the amount of dihydrate compound should be reduced to 6.6 mg per capsule. Capsules containing 0.6 mg of active substance may be prepared as described above; however, the amount of dihydrate should be reduced to 0.66 mg with 200 mg Polyethylene Glycol per capsule.

The intermediates and processes of the present invention are useful for preparing compounds having beneficial peripheral opioid antagonist activity. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

A) The crystalline compound 2 is the methyl ester.ester.

B) The crystalline compound 2 is (αS,3R,4R)-3-[[4-(3-hydroxyphenyl)-3,4 -dimethyt-α-(phenylmethyl)-1-piperidine propanoic acid, methyl ester hydrochloride.

C) The crystalline compound 2 is the ethyl ester.

D) The crystalline compound 2 is the HBr salt.

E) The lower alcohol is methanol.

F) The lower alcohol:water ratio is 50–60% lower alcohol and 50–40% water.

G) R^1 is C_1–C_4 alkyl.

H) The crystalline compounds of Formula 4 are the sesquimalate salt.

I) The crystalline compounds of Formula 4 are the hydrochloride acetone monosolvate form.

J) The substantially pure dihydrate of Formula 5 is 97% or more 2S, 3R, 4R dihydrate.

K) A pharmaceutical formulation comprising a dihydrate compound of Formula 5 and one or more pharmaceutically acceptable excipients.

L) A pharmaceutical formulation comprising a sesquimalate salt of a compound of Formula 4.

M) A method of using a compound of Formula 5 to treat irritable bowel syndrome.

N) A method of using one or more compounds of Formula 4 to treat irritable bowel syndrome.

O) A method for binding a mu receptor comprising administering an effective amount of a compound of Formula 5.

P) A method for binding a mu receptor comprising administering an effective amount of one or more compounds of Formula 4.

The preferred embodiments of this invention are represented by A-P.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

The concentration of reactants is not critical for the invention. The art worker can alter the concentration of the reactants to achieve the desired rate of reaction and product yield.

The length of time for carrying out the processes described is not critical. As is always the case in chemistry, the rate of the reaction depends on a variety of factors, such as the temperature and the exact compound which is to be prepared. The course of the reaction may be followed using methods such as thin layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography (GC) and nuclear magnetic resonance spectroscopy (NMR) to detect the degree of completion of the reaction. The operator may obtain maximum yields using the process by extending the reaction time. Alternatively, the operator may wish to obtain maximum throughput by cutting off the reaction at the point at which it reaches an economical degree of completion.

As used in the instant examples, the following terms have the meanings indicated. "HOBt" refers to 1-hydroxybenzotriazole hydrate. "THF" refers to tetrahydrofuran. "DMF" refers to dimethylformamide. "TEA" refers to triethylamine. "DCC" refers to dicyclohexylcarbodiimide.

PREPARATION 1

(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinepropanoic acid methyl ester

A round bottom flask was charged with THF (1000 mL) and (+)-3-(3,4-dimethyl-4-piperidinyl)phenol (70.46 g, 0.343 mol). The suspension was heated to 40°–45° C. and methyl acrylate (46.4 mL, 0.515 mol, 1.5 equiv) was added over three minutes. No change in temperature was observed.

The reaction was stirred at 45 ° C. and the progress monitored by HPLC. The reaction mixture remained cloudy. After four hours, the reaction mixture was cooled to room temperature and filtered through diatomaceous earth. The solvent and excess methyl acrylate were removed by concentration of the solution via rotary evaporation at 40° C. to a net weight of 120 g. The crude product was redissolved in THF (180 g) to give a 33.3 wt % solution for use in the process of Example 2.

Quantitative yield by HPLC. [α]s(20,D) 75.3° (C 1.01, MeOH), $[\alpha]^{20}_{365}$ 245.6° (c 1.01, MeOH). IR ($CHCl_3$): 3600, 3600–3100, 1732, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ0.72 (d, 3H, J=7.0 Hz), 1.30 (s, 3H), 1.59 (br d, 1H), 1.90–2.03 (m, 1H), 2.25–2.50 (m, 2H), 2.50–2.90 (m, 7H), 3.66 (s, 3H), 6.63 (dd, 1H, J=7.8, 2.0 Hz), 6.73 (br s, 1H), 6.81 (d, 1H, J=7.8 Hz), 7.15 (t, 1H, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$): δ16.1, 27.4, 30.8, 32.0, 38.4, 38.9, 49.9, 51.7, 53.9, 55.7, 55.8, 112.5, 112.6, 113.0, 113.2, 117.6, 117.7, 129.2, 151.6, 156.1, 173.4. UV (EtOH): λ_{max} 274 nm, ε2028; 202 nm, ε17350. MS (FAB): m/z 292 (100%, M+1), 292 (18%, M+), 218 (65%).

PREPARATION 2

Isobutyl glycine, p-toluenesulfonic acid salt

A round bottom flask was charged with toluene (600 mL), glycine (22.53 g, 0.30 mol), p-toluenesulfonic acid monohydrate (62.76 g, 0.33 mol, 1.1 equiv) and isobutyl alcohol (60 mL, 0.65 mol, 2.17 equiv). The heterogeneous reaction mixture was stirred and heated to reflux with a heating mantle to azeotropically remove the water as it was formed. After two hours the reaction mixture was homogeneous. After an additional 1.5 hours the reaction mixture was cooled to 50° C. and concentrated via rotary evaporation at 60° C. to a net weight of 135 g.

The residue (homogeneous oil) was dissolved in ethyl acetate (450 mL) while it was still warm and the solution transferred to a 3-necked round bottom flask equipped with a mechanical stirrer and a reflux condenser. Hexane (450 mL) was added to the solution with stirring at room temperature. The slurry was then heated to reflux to redissolve the solid and the solution allowed to cool slowly, with stirring. The solution was seeded at 38° C. to initiate crystallization. After cooling to room temperature the mixture was cooled to 5° C. and stirred for an additional hour. The product was isolated by filtration through a frittedglass funnel, air-dried for ½ hours and then dried overnight in a vacuum oven (40° C., 5 mm Hg). A total of 89.1 g (97.9%) of a white crystalline solid was obtained.

mp=77.2–79.6 ° C. pKa (67% aq. DMF)=7.68. IR ($CHCl_3$): 3300–2600, 3018, 2970, 1752, 1213, 1125, 1033, 1011 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ0.82 (d, 6 H, J=6.9), 1.79 (sept., 1 H, J=6.8), 2.33 (s, 3 H), 3.66 (br s, 2 H), 3.78 (d, 2 H, J=6.6), 7.10 (d, 2H, J=8.1), 7.72 (d, 2 H, J=8.2), 8.03 (br s, 3 H) . ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ18.9, 21.3, 27.4, 40.3, 72.0, 126.1, 128.9, 140.3, 141.4, 167.5.

Analysis for $C_{13}H_{21}NO_5S$:

Calculated: C, 51.47; H, 6.98; N, 4.62; S, 10.57.

Found: C, 51.74; H, 6.77; N, 4.76; S, 10.73.

EXAMPLE 1

(2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid 2-methylpropyl ester

A round bottomed flask was charged with (αS,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidine propanoic acid (20.11 g, 0.0522 mol, 1 equiv), a compound of Preparation 2 (17.60 g, 0.058 mol, 1.11 equiv), hydroxybenzotriazole monohydrate (7.83 g, 0.058 mol, 1.11 equiv) and dry tetrahydrofuran (144 mL). Triethylamine (8.08 mL, 0.058 mol, 1.11 equiv) was added to the mixture, followed by dicyclohexylcarbodiimide (11.97 g, 0.058 mol, 1.11 equiv) dissolved in tetrahydrofuran (60 mL). The mixture was stirred at 25° C. under nitrogen for two days. The completion of the reaction was monitored using HPLC. The slurry was cooled at 0° C. for two hours and then filtered. The filtrate was then evaporated to near dryness under reduced pressure (10 Torr) at 40° C. The oil was taken up in 250 mL of ethyl acetate. The organic layer was washed with 250 mL of a 0.5 M, pH 9.8 CO_3^{-2}/HCO_3^{-1} buffer solution. The pH was adjusted to 9.5–9.8. The organic solution was washed with 250 mL of saturated brine. The organic layer was dried over Na_2SO_4, cooled with stirring to −20° C. and allowed to stand, unstirred at −20° C. overnight (16 hr). The precipitated DCU was removed by filtration. The ethyl acetate was evaporated under reduced pressure (10 Torr) to yield 25.0 g (95%) of an amorphous solid.

IR ($CHCl_3$) 2897, 1740, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ8.94 (dd, 1H, J=2.0 Hz), 8.40 (bs, 1H), 7.20–6.93(m, 4H), 6.60–6.50 (m, 3H), 4.04, 3.95 (m, 2H), 3.80–3.65 (m, 2H), 3.16 (dd, 1H, J=13.8 Hz, J=4.4 Hz), 2.69 (bd, 1H, J=10.2 Hz), 2.63–2.41 (m, 4H), 2.40–2.15 (m, 4H), 1.84–1.71 (m, 2H), 1.42 (bd, 1H, J=12.4 Hz), 1.10 (s, 3H), 0.77 (d, 6H, J =6.9 Hz), 0.57 (d, 3H, J=6.9 Hz), ^1H NMR (300 MHz, DMSO-d_6): δ9.17 (bs, 1H), 8.40 (bt, 1H, J=2.0 Hz), 7.26–7.14 (m, 4H), 7.04 (t, 1H, J=7.8 Hz), 6.63 (m, 2H), 6.52 (d, 1H, J=8.1 Hz), 3.81–3.79 (m, 4H), 2.90–2.43 (m, 6H), 2.37 (d, 1H, J=12.4 Hz), 2.33–2.03 (m, 3H), 1.95–1.65 (m, 2H), 1.43 (d, 1H, J=12.4 Hz), 1.17 (s, 3H), 0.85 (d, 6H, J=6.7 Hz) 0.65 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ174.03, 169.78, 157.05, 151.71, 140.08, 128.80, 128.71, 125.77, 115.93,112.36, 112.06, 69.96, 59.73, 54.95, 49.87, 44.24, 40.59, 38.03, 37.83, 35.61, 29.93, 27.19, 27.08, 18.72 15.79; MS (FD) m/z 481 (M+); $[\alpha]^{25}_{589}$ +57.23°, $[\alpha]^{25}_{365}$ +170° (MeOH, c=1.01); UV (MeOH) 274.4 nm (ε=2093), 202.8 nm.

Analysis for $C_{29}H_{40}N_2O_4$:
Calculated: C, 72.47; H, 8.39, N, 5.83.
Found: C, 72.49; H, 8.59; N, 5.63.

EXAMPLE 2

(αS,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoic acid methyl ester hydrochloride

A round bottom flask was purged with nitrogen and charged with THF (100 mL) and a 2.0 M solution of LDA (17.6 mL, 35.18 mmol, 2.05 equiv). The solution was cooled to −30° C. and the solution of a compound of Preparation 1 (15.24 g, 17.16 mmol, 1.0 equiv, 32.8 wt % in THF) was added over 20 minutes while maintaining the temperature between −26° and −28° C.

After stirring for 15 minutes at −25° C., benzyl bromide (5.81 g, 34.32 mmol, 2.0 equiv) was slowly added while maintaining the temperature between −17° and −20° C. The reaction mixture was stirred at −15° to −20° C. for three hours. ((αS,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoic acid methyl ester/(αR,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinepropanic acid methyl ester=97/3).

The reaction mixture was quenched with 1 N HCl (22 mL, 22 mmol). The pH was adjusted from 10.6 to 9.5 with 12 N HCl (2.3 mL) and the low temperature bath was removed. Heptane (50 mL) was added and the layers separated. Methanol (25 mL) was added to the organic layer and the solution cooled. Anhydrous HCl (1.3 g) was added to the solution while maintaining the temperature below 5° C. until the mixture was acidic. The hydrochloride salt precipitated during the addition. The mixture was concentrated to a net weight of 32.58 g. Methanol (36 mL) was then added to the oily concentrate and after a few minutes a precipitate formed. The mixture was stirred overnight at room temperature.

After cooling to 0° C. for 1.25 hours the precipitate was filtered, the flask rinsed with 10 mL of the filtrate, and the cake washed with cold methanol (10 mL). The solid was dried to give 2.93 g (40.9% yield) of a white powder.

Analysis by HPLC showed that the product was a 86:14 mixture of stereoisomers.

The crude hydrochloride salt (2.75 g) was added to methanol (13.75 mL) and the slurry heated at reflux for two hours. The mixture was cooled to about 0° C. The precipitate was filtered, the flask was rinsed with liltrate and the cake was washed with cold methanol (1.5 mL). The product was dried to yield 2.32 g of a white solid (84.4% yield).

Overall Yield: 34.5% (alkylation & hot reslurry)

Purity: 96.2% ((αS, 3R, 4R) -4-(3-hydroxyphenyl)-3,4-dimethyl-α- (phenylmethyl)-1-piperidinepropanoic acid methyl ester hydrochloride, 2.9% (αR, 3R, 4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-(α-(phenylmethyl)-1-piperidinepropanoic acid methyl ester hydrochloride and 0.7% (αS, 3R, 4R)-4-(3-hydroxyphenyl)-3,4 -dimethyl-α-(phenylmethyl)-1-piperidinepropanoic acid monohydrate (HPLC area %). mp 230°–232 ° C. (dec), IR (KBr): 3174, 1732, 1620, 1586, 1276, 785,749, 706 cm^{-1}. ^1H-NMR (DMSO-d_6): d [0.78 (d, 0.85 ×3H, J=7.2 Hz) & 1.02 (d, 0.15×3H, J=7.2 Hz), diastereomeric salts], [1.28 (s, 0.15×3H), 1.34 (s, 0.85×3H), diastereomeric salts], 1.76 (br d, 1H), 2.10–2.48 (m, 2H), 2.75–3.65 (m, 12H), 6.60–6.90 (m, 3H), 7.11 (t, 1H, J=7.8 Hz), 7.15–7.35 (m, 5H), 9.43 (br s, 1H), 9.75 (br s, 1H).

MS (FD): m/z 381 (100%, M-HCl).

Analysis for $C_{24}H_{32}ClNO_3$:
Calculate: C, 68.97; H, 7.72; N, 3.35; Cl,8.48.
Found: C, 69.27; H, 7.84; N, 3.42; Cl, 8.38.

EXAMPLE 3

(+)-((αS, 3R, 4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoic acid monohydrate

Deionized water (230 mL) was charged to a round bottom flask along with a 50% w/w sodium hydroxide solution (20.02 g, 250 mmol, 4.2 equiv). In one portion of the product of Example 2 (25.0 g, 60 mmol, 1 equiv) was added to the flask. The mixture was stirred at room temperature and filtered. The filter paper was rinsed with 33 mL of a 1 N sodium hydroxide solution. The

solution was transferred to a round bottom flask suitable for a vacuum distillation. Methanol (240 mL) was charged to the solution. The pH of the solution was adjusted to 6.0 using concentrated hydrochloric acid (32.14 g). The methanol was removed at reduced pressure (100–200 mm Hg) and temperature (45°–50° C.). The methanol was removed until the weight of the concentrate was approximately 313 g. The slurry was allowed to stir for four hours. The pH of the solution was readjusted to 6.0 and the slurry was then cooled at 0°–5° C. for 1.5 hours. The desired product was filtered and washed three times with 50 mL of deionized water. The product was then dried. The desired monohydrate product was isolated as a white granular solid and weighed 21.3g for a 92% yield.

mp 178°–180 ° C. (dec.).

^{1}H NMR (300 MHz, DMSO) δ0.64 (d, 3H, J=6.9 Hz), 1.19 (s, 3H), 1.51 (d, 1H, J=13.1 Hz), 1.97–2.00 (m, 1H), 2.11 (td, 1H, J=3.6 Hz, 12.7 Hz), 2.34–2.95 (m, 9H), 6.54 (d, 1H, J=8.1 Hz), 6.66 (m, 2H), 7.06 (t, 1H, J=7.9 Hz), 7.14–7.28 (m, 5H), 9.22 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO) δ15.5, 26.9, 29.5, 35.2, 37.5, 37.7, 42.7, 49.7, 53.7, 58.8, 112.2, 112.3,115.9, 126.0, 128.2, 128.7, 128.9, 139.4,151.2, 157.1, 175.1. UV (MeOH) λmax 203, ε17,860; 275, λ2356. MS (FD) m/z 368. IR (KBr) 3360, 3272, 2967, 1622, 1585, 1363, 844 cm^{-1}. $[\alpha]^{20}_{365}$ 304 (C 1.01, MeOH). KF=4.07% (Calcd for monohydrate: 4.70%) .

Analysis for $C_{23}H_{31}NO_4$:

Calculated: C, 71.66; H, 8.10; N, 3.63.

Found: C, 72.29; H, 8.10; N, 3.71.

EXAMPLE 4

(2s, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid -methylpropyl ester sesquimalate salt (1:1.5)

A compound of Example 1, (2.5 g, 5.2 mmol, 1.0 equiv) was dissolved in 50 mL of ethyl acetate. L-malic acid (1.03 g, 7.8 mmol, 1.5 eq) was added to the mixture. After the L-malic acid was dissolved by stirring, the solution was heated to 70° C. and 4.0 mL of acetone was added. The solution was crystallized. The product was isolated by filtration. The filter cake was washed with ethyl acetate. The salt was dried until the ethyl acetate levels were below 1%. The title compound was isolated as a white crystal. The sample was analyzed using x-ray powder diffraction. mp 94°–950C.

IR (KBr) 3346.92, 2972.68, 1741.94, 1601.12 cm^{-1};

^{1}H NMR (300 MHz, DMSO-d_6) δ9.70 (bs, 1H), 8.47 (t, 1H, J=1.9 Hz), 7.27–7.13 (m, 4H), 7.06 (t, 1H, J=7.9 Hz), 6.67 (d, 1H, J=8.0 Hz), 6.63 (s, 1H), 6.53 (dd, 1H, 8 Hz, J=1.7 Hz), 4.18 (t, 1.5H, J=5.8 Hz), 3.82–3.78 (m, 3H), 3.33–1.80 (m, 16 H), 1.48 (bd, 1H, J=13.0 Hz), 1.18 (s, 3H), 0.85 (d, 6H, J=6.7 Hz), 0.64 (d, 3H, J=6.9 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ175.63, 175.42, 171.44, 158.66, 138.63, 138.60, 130.50, 130.23,129.66, 128.02, 114.07, 114.05, 14.01, 113.94; MS (FD) m/z 481 (M+); UV (MeOH) 272.8 nm (e=797), 202.4 nm (ε=20576);

Analysis for $C_{70}H_{98}N_4O_{23}$:

Calculated: C, 61.65; H, 7.38; N, 4.10; O, 26.98.

Found: C, 61.40; H, 7.23; N, 4.1; O, 26.66.

EXAMPLE 5

(2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid dihydrate

A solution of a compound of Example 1 (12.5 g, 0.026 mol, 1.0 equiv) in 315 mL of 3A ethanol was charged to round bottom flask. Water (74.0 mL) was added to the mixture. Aqueous solution of sodium hydroxide ((1.0 M) 0.077 mol, 3.0 equiv) was added dropwise over 10-15 minutes at 25°–30° C. The solution was stirred and then filtered. The pH of the solution was adjusted from 12.50 to 6.00 by addition of concentrated hydrochloric acid. The solution was seeded and (2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethYl-1-piperidinyl]methyl]-1-oxo -3-phenylpropyl]amino]acetic acid began to precipitate within 10–15 minutes. The crystallization was stirred at 25° C. for two hours and then (2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethYl-1-piperidinyl]methyl]-1-oxo -3-phenylpropyl]amino]acetic acid was filtered under slight suction to a wet cake. The crystals were slurried with 60 mL of water and filtered to a hard cake under suction. The crystals were dried to the dihydrate overnight (16 hours) under open air at 33% relative humidity at 25° C. by pulling air over the product in the filter funnel under slight suction. The title compound was isolated in 85% yield (10.2 g), from (αS,3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl -α-(phenylmethyl)-1-piperidine propanoic acid monohydrate, as white crystals with a sharp melting point of 208° C. The sample was analyzed using x-ray powder diffraction.

IR (KBr) 3419, 3204, 3028, 1684, 1591 cm^{-1};

^{1}H NMR (300 MHz, DMSO - d_6) δ9.18 (bs, 1H), 8.34 (t, 1H, J=5.5 Hz) 7.26–7.12 (m, 6H), 7.05 (t, 1H, J=7.9 Hz), 6.67 (d, 1H, J=8.0 Hz), 6.63 (s, 1H), 6.52 (dd, 1H, J=8.0 Hz, J=1.8 Hz), 3.65 (d, 2H, J=5.6 Hz), 2.89–2.10 (m, 14H), 1.91 (bd, 1H, J=6.7 Hz), 1.18 (s, 3H), 0.64 (d, 3H, J=6.9 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ173.54, 71.30, 157.05, 151.28, 139.83, 128.83, 128.73, 128.05, 125.82, 115.97, 112.14, 59.62, 54.59, 49.92, 43.75, 41.12, 39.95, 39.67, 39.39, 39.12, 38.84, 37.80, 37.73, 35.42, 29.68, 27.04, 15.54; MS (FD) m/z 425 (M+-2H_2O): UV (MeOH) 275.0 (ε=2246), 202.6 (ε=22709.4); $[\alpha]^{25}_{365}$= −1.18 (MeOH, c=1.0);

Analysis for $C_{25}H_{36}N_2O_6$:

Calculated: C, 65.20; H, 7.88; N, 6.08; O, 20.84.

Found: C, 64.96; H, 7.74; N, 6.10; O, 20.82;

EXAMPLE 6

(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid dihydrate

Ethanol (2400 mL, 3A) and a compound of Example 4 (146 g with 5% EtOAc, 138.7 g pura, (0.203 mol, 1.0 equiv., 0.085 molal) were charged to a round bottom flask. A 1.0 M aqueous solution of sodium hydroxide (1200 mL, 1.2 mol, 5.9 equiv.) was added dropwise over 20 minutes at 25°–30° C. The solution was stirred and then filtered. The pH of the solution was adjusted from 12.96 to 6.00 by addition of concentrated hydrochloric acid. The solution was seeded and (2S, 3R, 4R) [[2- [[4- (3-hydroxyphenyl) -3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid began to precipitate within 10–15 minutes. The crystallization was stirred at 25° C. for two hours. The slurry was cooled to 0° C. and stirred. The (2S,3R,4R)[[2-[[4-(3-hydroxyphenyl) -3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid product was filtered under slight suction to a wet cake. The crystals were slurried with 500 mL of 25° C. water with stirring, followed by slight suction, reslurried with 500 mL of water, and filtered to a hard cake under suction. The

crystals were dried to the dihydrate overnight under open air at 35% relative humidity at 25° C. by pulling air over the product in the filter funnel under slight suction. The title compound was isolated in 93% (88 g) yield, as white crystals with a sharp melting point of 208 ° C.

Analysis for $C_{25}H_{36}N_2O_6$:

Calculated: C, 65.20; H, 7.88; N, 6.08; O,20.84.

Found: C, 65.38; H, 7.87; N, 6.25; O, 20.90;

EXAMPLE 7

(2S,3R,4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]a-cetic acid 2-methylpropyl ester hydrochloride aetone monosolvate

A 6.0 g sample of a compound of Example 1 was dissolved in 60.0 mL of dry acetone. A 0.45 g portion of HCl gas (0.98 equiv.) dissolved in 30.0 mL of dry acetone was added dropwise at 25° C. The HCl gas in acetone was added dropwise until the pH was pH 3. When the pH reached 3, a second 1.0 mL aliquot of a compound of Example 1, at the same concentration as the starting solution, was added. Precipitate formed. The reaction was stirred at 25° C. for one hour and then cooled to 0° C. The reaction was stirred at 0° C. for two hours. The desired (2S,3R,4R)[[2-[[4-(3-hydroxyphenyl) -3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid 2-methylpropyl ester hydrochloride salt was filtered with pressure filtration using nitrogen. The (2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl -1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid 2-methylpropyl ester hydrochloride salt was dried by streaming nitrogen over the liltrate to form the acetone monosolvate. The acetone monosolvate was characterized by capillary gas chromatographic analysis which showed 9.3%-9.97% (by weight) acetone. (Theoretical 10 percent). The product was characterized by removal of the acetone molecule of solvation.

The hydrochloride acetone monosolvate was dried further using a vacuum oven at 50° C. for 2 to 3 days. Formation of the hydrochloride monohydrate was affected by spreading the crystals over a large surface at 25° C. in 40% relative humidity for 2 days.

Yield was >85% with purity around 99.3% by reversed-phase HPLC.

mp 70°-75 ° C.; IR (KBr) 3217.7, 3063.4, 2965.0, 1749.7, 1671.5;

^{1}H NMR (300 MHz, DMSO-d_6) δ9.45 (bs, 1H), 9.37 (s, 1H), 8.94, (t, 0.85 H, J=1.5 Hz), 8.92 (t, 0.15H, J=1.5 Hz), 7.28-7.20 (m, H), 7.09 (t, 1H, J=7.8 Hz), 6.67-6.56 (m, 3H), 3.83-3.76 (m, 4H), 3.47-3.10 (m, 5H), 2.83 (dq, 2H, J=18.0 Hz, J=5.5 Hz, J=2.0 Hz), 2.7-2.0 m, 5H), 1.82 (sept, 1H, J=6.7 Hz) 1.70 (d, 1H, J=12.0 Hz), 1.29 (s, 0.85 H), 1.24 (s, 0.15 H) 0.99 (d, 0.45 H, J=7.4 Hz), 0.85 (d, 6 H, J=6.6 Hz), 0.71 (d, 2.55 H, J=7.3 Hz); ^{13}C NMR (75.4 Hz, DMSO-d_6) δ172.7, 169.8, 157.4, 149.4, 129.3, 128.3, 121.6, 118.6, 115.7, 112.9, 112.3, 53.9, 57.1, 70.2, 48.1, 46.4, 40.8, 37.3, 36.9, 27.3, 27.0, 26.5, 18.8, 15.1; UV (MeOH) 274 (ε=2738), 202.2 (ε=28413); MS (FD) 481 (M^+-HCl-H_2O);

Analysis for $C_{29}H_{41}N_2O_4$-H_2O:

Calculated: C, 65.09; H, 8.10; N, 5.23; O, 14.95; Cl, 6.63

Found: C, 65.06; H, 7.92; N, 5.27; O, 15.19; Cl, 6.92

EXAMPLE 8

(αS, 3R, 4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoic acid ethyl ester hydrochloride

A sample of (+)-3-(3,4-dimethyl-4-piperidinyl)-phenol (50.0 g, 243.5 mmol, 1.0 equivalent) was charged to a round bottom flask. Tetrahydrofuran (1 L) and ethyl acrylate (33.0 mL, 304.4 mmol, 1.25 equivalents) were added and the heterogeneous reaction mixture was stirred for several days at room temperature. The reaction mixture was filtered through diatomaceous earth and the transparent solution was stripped to a viscous amber oil weighing 75.0 g. A portion of the amino ester (1.16 g, 3.80 mmol, 1.0 equivalent) was redissolved in 10 mL of tetrahydrofuran (THF) and added to a −75 ° C. solution of lithium diisopropylamide (3.90 mL, 7.80 mmol, 2.05 equivalents) in THF (20 mL). The addition took approximately five minutes. The slurry was then stirred at −70 ° C. for 15 minutes and benzyl bromide (0.47 mL, 3.99 mmol, 1.05 equivalents) was added. The reaction was allowed to warm to −25° to −30 ° C. and stirred for 3 hours. The reaction was quenched with 10 mL of saturated ammonium chloride and 10 mL of H_2O and 20 mL of ethyl acetate. The aqueous layer was separated. The organic layer was washed with saturated brine solution. The organic was then dried over $MgSO_4$. The mixture was filtered and the resulting solution was then rotary evaporated to yield a yellow oil weighing 1.80 g. The mixture of product and starting material was then flash chromatographed with a mixture of ethyl acetate and hexane to isolate 1.07 g (71%) of the ethyl ester.

The ethyl ester from above (14.8 g, 37.4 mmol) was then dissolved in 150 mL of ethanol. Anhydrous hydrogen chloride was sparged into the solution and the ethanol was removed by rotary evaporation. The solid was then triturated with 50 mL of ethyl acetate and filtered. The solid was dried overnight at 30° C. to isolate 12.25 g of the hydrochloride (76%, melting point of 179°-181 ° C.). The diasteromer ratio was 49% αS, 3R, 4R (desired diastereomer) to 51% αR, 3R, 4R (undesired diastereomer).

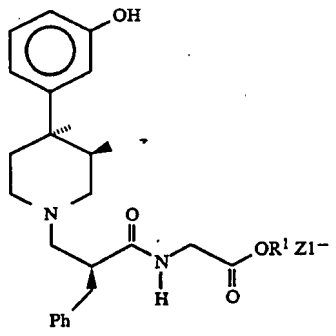
The hydrochloride salt (1.02 g) was slurried in 5 mL of ethanol and refluxed for 3 hours. The mixture was allowed to cool back to room temperature and stirred. The mixture was stirred at 0° C. for 1 hour and then filtered. The salt was dried overnight at 40° C. The while solid isolated weighed 0.48 g (47%). The diastereomer ratio was 76% αS, 3R, 4R to 24% αR, 3R, 4R.

The hydrochloride sail (0.42 g) was slurried in 6 mL of ethanol and heated to reflux for 2 hours and then cooled back to room temperature and stirred. The slurry was cooled to 0° C. for 1 hour and filtered. The solid was dried wand 0.31 g (74%) of the salt was obtained. The diastereomer ratio was 92% αS, 3R, 4R to 8% αR, 3R, 4R.

A portion of the salt (0.24 g) was slurried a third time in 2.5 mL of ethanol. The mixture was healed at reflux for three hours and then allowed to cool back to room temperature and stirred. The slurry was cooled to 0° C. for 1 hour and then filtered. The solid was dried. The diastereomerically pure (98% αS, 3R, 4R) hydrochloride salt of the ethyl ester weighed 0.23 g (96%).

We claim:

1. A crystalline compound of the Formula 20



(20)

wherein R^1 is C_1–C_6 alkyl; Z1− is selected from the group consisting of hydrochloride, malate, and sesquimalate;

wherein when Z1− is sesquimalate then 3 molecules of malate are associated with 2 molecules of 20; and

when Z1− is hydrochloride then each molecule of 20 is solvated with one molecule of acetone.

2. A crystalline compound of claim 1 wherein Z1− is hydrochloride.

3. A crystalline compound of claim 1 wherein Z1− is sesquimalate.

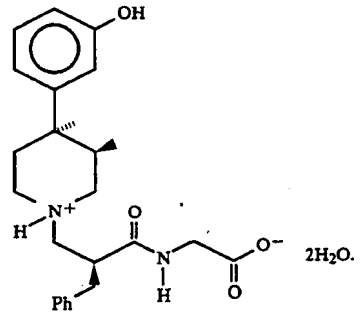
4. A crystalline compound of claim 1 wherein the compound of Formula 1 is (2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid 2-methylpropyl ester.

5. A crystalline compound of claim 2 wherein the compound is (2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid 2-methylpropyl ester hydrochloride acetone monosolvate.

6. A crystalline compound of claim 3 wherein the compound is (2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid 2-methylpropyl ester.

7. A crystalline compound of claim 1 wherein the compound is (2S, 3R, 4R)[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic acid 2-methylpropyl ester malate.

8. A crystalline dihydrate compound of the Formula



(5)

$2H_2O$.

9. A compound of claim 8 wherein the crystalline dihydrate compound is at least 97% (2S,3R,4R)dihydrate.

10. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 1.

11. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 8.

12. A method for treating a condition selected from the group consisting of irritable bowel syndrome, idiopathic constipation, and non-ulcer dyspepsia; comprising administering an effective amount of a compound of claim 1.

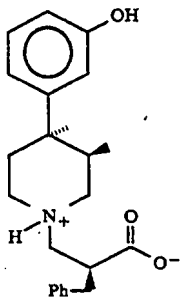
13. A method for treating a condition selected from the group consisting of irritable bowel syndrome, idiopathic constipation, and non-ulcer dyspepsia; comprising administering an effective amount of a compound of claim 8.

14. A pharmaceutical formulation comprising an effective amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable excipients.

15. A pharmaceutical formulation comprising an effective amount of a compound of claim 8 in combination with one or more pharmaceutically acceptable excipients.

16. A formulation of claim 15 wherein the formulation is a hard gelatin capsule.

17. A process for preparing a crystalline monohydrate compound of Formula 3



(3)

comprising the crystallization of 3 from a solvent comprised of about 50% methanol and about 50% water (by weight).

* * * * *

EXHIBIT 4

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United States Patent and Trademark Office

Patent Bibliographic Data					06/02/2008 11:26 AM
Patent Number:	5434171		**Application Number:**	08164074	
Issue Date:	07/18/1995		**Filing Date:**	12/08/1993	
Title:	PREPARATION OF 3,4,4-TRISUBSTITUTED-PIPERIDINYL-N-ALKYLCARBOXYLATES AN				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	01/03/2007 12/30/2002 12/07/1998 12/02/1998	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payor Number Assigned. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	ELI LILLY & COMPANY PATENT DIVISION, #1104 LILLY CORPORATE CENTER INDIANAPOLIS,, IN 46285				

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United States Patent and Trademark Office

Patent Maintenance Fees			06/02/2008 11:29 AM EDT
Patent Number:	5434171	Application Number:	08164074
Issue Date:	07/18/1995	Filing Date:	12/08/1993
Window Opens:		Surcharge Date:	
Window Closes:		Payment Year:	
Entity Status:	LARGE		
Customer Number:	139		
Street Address:	ELI LILLY & COMPANY PATENT DIVISION, #1104		
City:	INDIANAPOLIS,		
State:	IN		
Zip Code:	46285		
Phone Number:	(317) 261-3470		
Currently there are no fees due.			

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EXHIBIT 5

MWT OCT 21 '93

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 43,693

OCT 18 1993

Eli Lilly and Company
Attention: M.W. Talbott, PhD
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Talbott:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 43,693

Sponsor: Eli Lilly and Company

Name of Drug: LY246736 Dihydrate Capsules

Date of Submission: October 11, 1993

Date of Receipt: October 12, 1993

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon

as possible and in no event later than 10 working days after initial receipt of information; reporting any unexpected fatal or life-threatening experience to FDA by telephone no later than three working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please call me at (301) 443-0487.

Sincerely yours,

Kati Johnson

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

EXHIBIT 6

Lilly

3613.3

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

COPY

February 3, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Attn.: Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857-1706

IND 43,693 - Compound LY246736 Dihydrate Capsules
Serial No.: 013

This correspondence is to notify you that on November 5, 1996, Eli Lilly and Company entered into an agreement with Roberts Laboratories Inc., a wholly owned subsidiary of Roberts Pharmaceutical Corporation, granting them the right to development of the aforementioned compound. Consequently, Eli Lilly and Company is transferring sole sponsorship of IND 43,693 to Roberts effective February 1, 1997. Roberts will assume all responsibilities of maintaining the IND and will be the official correspondent for any future communications with the FDA. All records have been transferred from Lilly to Roberts. There are no ongoing clinical trials at this time.

Please address any questions you may have for Lilly to Dr. Kelly Freeman at (317) 276-1337. Questions for Roberts should be addressed to Mr. Drew Karlan at (908) 389-1182. Thank you for your continued assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures

GTB:dmm

EXHIBIT 7

ROBERTS PHARMACEUTICAL CORPORATION

June 24, 1998

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Rm. 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 017: Letter of Authorization to IND

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to refer to IND 43,693, for LY246736 Dihydrate Capsules, on behalf of ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

ADOLOR Corporation intends to submit their own IND for the purpose of conducting Phase I clinical studies under a licensing agreement with Roberts Laboratories Inc.

This authorization will remain in effect for a period of one calendar year from the date of this letter.

If you have any questions regarding this letter, please do not hesitate to communicate with me.

Sincerely,

Drew Karlan

Drew Karlan, V.P.
Worldwide Regulatory Affairs

DR/lb

Enclosure: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

LY736LOA.FDA

EXHIBIT 8

ROBERTS PHARMACEUTICAL CORPORATION

June 17, 1999

COPY

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Rm. 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 019: Letter of Authorization to IND

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to refer to IND 43,693, for LY246736 Dihydrate Capsules, on behalf of ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

This authorization will remain in effect for a period of one calendar year from the date of this letter.

If you have any questions regarding this letter, please do not hesitate to communicate with me.

Sincerely,

Alvin Howard, Vice President
Worldwide Regulatory Affairs

AH/lep

Enclosure: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

EXHIBIT 9

ROBERTS
RMACEUTICAL
CORPORATION

COPY

March 22, 2000

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 021: Transfer of IND Ownership to ADOLOR Corporation

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to transfer all rights to IND 43,693 (LY246736 Dihydrate Capsules) from the existing holder of the IND, Roberts Laboratories Inc. to ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

There has been no activity regarding IND 43,693 since Roberts acquired the rights to this product from Eli Lilly & Co. on February 1, 1997. There are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules under this IND. The last Annual Report was submitted to the IND on March 3, 1999 (Serial No. 018).

If you have any questions regarding this letter, please do not hesitate to communicate with me at (732) 676-1200, ext. 2074.

Sincerely,

Alvin Howard, Vice President
Regulatory Affairs

RR\lep
Enc.: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

LY736transfer

EXHIBIT 10

adolor CORPORATION

343 Phoenixville Pike, Malvern, PA 19355 TEL (610) 889-3470 FAX (610) 889-5760

September 21, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-180
5600 Fishers Lane
Rockville, MD 20857

RE: IND #43,693
Serial No. 023 - **Response to FDA Request for Information**

Dear Dr. Talarico:

Sponsorship of the referenced IND was transferred from Roberts Laboratories, Inc. to Adolor Corporation on March 22, 2000, in Serial No. 021. On March 29, 2000, in Serial No. 022, Adolor accepted all agreements, promises and conditions made by Roberts that were still in effect at the time of the transfer. Pursuant to that transfer and acceptance, Mr. Paul Levine requested on September 12, 2000, the following information to complete the change of sponsorship procedure. His request is highlighted below with our response.

1. **"A commitment to inform all active investigators of the change in sponsorship and to obtain from them updated forms FDA 1572 and commitments to you as the new sponsor."**

Adolor does commit to inform all active investigators of the change in sponsorship and to obtain from them updated forms FDA 1572 and commitments to us as the new sponsor. However, Roberts withdrew this IND in Serial No. 20 on December 3, 1999, and there were no active investigators or study subjects taking the investigational drug at the time of the transfer for Adolor to notify. The IND has not been reactivated nor amended to provide for clinical trials and active investigations.

2. **"A list of all active investigators or a statement that they are the same as currently listed in the IND, if that is the case."**

As noted above, there are no active investigators in the withdrawn IND. Adolor has not amended the IND other than to accept the transfer. There have been no additions or deletions of the investigators, as no studies are being conducted under this IND. The last annual report prior to Robert's withdrawal of the IND stated that there had been no activity conducted under the IND during the report period of April 8, 1998 through September 30, 1998 (please refer to Serial No. 018: Annual Report). This IND has been used by Adolor as reference only.

3. "Submission of any change in protocol or other study parameters."

When the investigational compound, LY246736 Dihydrate capsules, was licensed to Adolor for development, Adolor filed its own IND, No. 56,533, which is currently active and refers to the investigational drug as ADL 8-2698. The Roberts IND No. 43,693 (formerly sponsored by Eli Lilly & Co.) was referenced in Adolor's IND filing. Thus, Adolor made no change to protocols originally filed to the Roberts IND. If Adolor's clinical studies under its IND progress to an NDA, any relevant sections and reports from IND 43,693 will be filed in the NDA.

If you have any questions or need additional information, please contact me at 610-889-3472 by phone or 610-889-5760 by facsimile.

We understand that this IND and all information contained therein, unless otherwise made public by Adolor Corporation, is CONFIDENTIAL.

Sincerely,

ADOLOR CORPORATION

Linda Y. Harver

Linda Y. Harver, R.Ph., J.D.
Vice President, Regulatory Affairs

EXHIBIT 11

CONFIDENTIAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 7, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-~~4005~~ 7450
Subject: Filing Letter, NDA 21-775	

Total no. of pages including cover:

Comments: Please find attached a copy of your Filing Letter for Entereg (Alvimopan) Capsules. In addition, please note that your Application has been classified as a Standard review, therefore, your PDUFA goal date will be April 25, 2004.

Should you have questions, please contact me at 301-827-7450.

Best regards.

Document to be mailed: √ YES NO

CONFIDENTIAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-775

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms. Harver:

Please refer to your June 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (Alvimopan) Capsules.

We also refer to your submissions dated May 4, 2004 and May 27, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 24, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues from an overview of the submission:

1) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in the primary efficacy endpoint [the time to tolerate the first solid meal and (the time to the first bowel movement or first flatus)] in only one (313) of the four Phase III efficacy trials (302, 308, 313, and 306).

2) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in a secondary endpoint (time to discharge written) in only two (313 and 308) of the four Phase III efficacy trials.

3) In Trial 313, the demonstration of a positive primary efficacy endpoint may have been due to the poor placebo response.

Therefore, we are concerned that the efficacy results for 12 mg of Entereg may not be adequate for the proposed indication.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation
Drug Products, HFD 180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
9/7/04 03:20:40 PM

EXHIBIT 12

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-775

NDA APPROVAL

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your new drug application (NDA) dated August 9, 2007, received August 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entereg (alvimopan) Capsules, 12 mg.

We acknowledge receipt of your submissions dated January 18, October 18, December 18 and 28, 2007, January 10, 17, 25, February 7, March 5 and 6, April 15, 17, 22, 29, and May 1, 2, 14, and 20, 2008.

The August 9, 2007 submission constituted a complete response to our November 3, 2006 action letter.

A meeting of FDA's Gastrointestinal Drugs Advisory Committee was held on January 23, 2008 to discuss the safety and effectiveness of Entereg.

This new drug application provides for the use of Entereg (alvimopan) Capsules, 12 mg, for the acceleration of time to gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are deferring submission of your pediatric studies for ages 0 months to 16 years until after the completion of your postmarketing required study, which is scheduled for completion

December 31, 2012, because this product is ready for approval in adults and additional safety data in adults are needed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these required postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age greater than 1 month up to 16 years undergoing bowel resection surgery. The study will measure the time to first tolerated feed, population pharmacokinetic parameters, the proportion of postoperative days with stool passed while in hospital, length of hospital stay, the need for postoperative nasogastric tube insertion for symptoms of postoperative ileus, and safety.

Protocol Submission:	December 2012
Study Start:	June 2013
Final Report Submission:	June 2016

2. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age 0 to 1 month undergoing bowel resection surgery. The study will measure population pharmacokinetic parameters, safety, and time to first tolerated feed while in the hospital.

Protocol Submission:	December 2016
Study Start:	June 2017
Final Report Submission:	June 2019

Submit all final study reports to your NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk, that is, an imbalance in the number of myocardial infarctions in Entereg-treated patients receiving long-term treatment for opioid-induced bowel dysfunction.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk of, and to monitor the incidence of, myocardial infarctions in Entereg-treated patients undergoing surgery compared to patients receiving a placebo.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial.

You are required to conduct the following clinical trial:

1. A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management or postoperative ileus in patients undergoing radical cystectomy.

The timetable you submitted on April 22, 2008 states you will conduct this trial according to the following timetable:

Protocol Submission:	June 2008
Trial Start:	March 2009
Final Report Submission:	June 2012

Submit the protocol to your IND 56,553 with a cross-reference letter to this NDA 21-775. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

You are required to report periodically to FDA on the status of this postmarketing study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Entereg.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with 505-1 of the FDCA, we have determined that a REMS is necessary for Entereg (alvimopan) Capsules, 12 mg, to ensure that the benefits of the drug outweigh the risks of myocardial infarction. Pursuant to section 505-1(f)(1), we have also determined that Entereg can be approved only if the elements necessary to assure safe use are required as part of a REMS to mitigate a specific serious risk, myocardial infarction, listed in the labeling of the drug.

Your proposed REMS, submitted on May 14, 2008 and resubmitted May 20, 2008, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, a timetable for assessments, and assessments of the REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS) Submission

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-775."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 1, 2008 submission containing final printed carton and container labels.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We acknowledge your May 2, 2008 commitment to expedited reporting of ischemic cardiovascular events, defined as: acute myocardial infarction, new onset or unstable angina, congestive heart failure, congestive cardiac failure, cerebrovascular accident (CVA), transient ischemic attach (TIA), cardiac arrest, and sudden death.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
5/20/2008 02:44:17 PM

EXHIBIT 13

Supplement to Response (11): Chronological Listing of Significant Activities Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period With Respect to the Approved Product

Date	IND/NDA	Serial or Amendment #	Activity
10/11/1993	IND 43,693		Lilly submission of IND for LY246736 Dihydrate.
10/12/1993	IND 43,693		FDA letter of October 18, 1993 acknowledging receipt of IND 43,693 on October 12, 1993.
11/11/1993	IND 43,693		Effective date of IND 43,693 under § 505(i)
01/25/1994	IND 43,693		FDA letter to Lilly suggesting amendment to clinical protocol.
02/09/1994	IND 43,693	#001	Pg. 2163 – Amendments a & b to the Dose-Escalation Safety Trial.
02/09/1994	IND 43,693	#002	Lilly letter responding to FDA January 25, 1994 letter requesting modification of Phase I dose-escalation study to allow for 48 hours between single escalating doses, further stating that the clinical study had already been partially completed without incident.
05/16/1994	IND 43,693		Protocol amendment and notice of new investigator, including highlights of results of prior protocol.
05/16/1994	IND 43,693	#003	Pg. 2185 – New Protocol No. H3G-LC-BGGB: "Dose-Escalation Trial in Patients with Irritable Bowel Syndrome."
05/19/1994	IND 43,693	#004	Pg. 2219-ADME Report No. 7: "Plasma Concentrations of LY246736 Following the Oral Administration of LY246736 Dihydrate to Fischer 344 Rats".
08/12/1994	IND 43,693	#005	Pg. 2229 – New Protocol No. H3G-LC-BGGC: "LY246736 – Multiple-Dose Trial in Subjects with Loperamide-Induced Constipation".
12/08/1994	IND 43,693	#006	Pg. 2264 – "Information Amendment: Pharmacology/Toxicity" - Toxicology Report No. 14: "A combined Segment I and Segment II Study of LY246736 Dihydrate Administered Orally to CD Rats". (Study No. R12693 and R12793)
01/06/1995	IND 43,693	#007	Annual report for the period ending November 10, 1994, noting that 3 protocols had been submitted, 2 trials completed and 2 clinical pharmacology trials were started and completed by November 10, 1994.
01/12/1995	IND 43,693		Notice from FDA of late annual report by Lilly.

Date	IND/NDA	Serial or Amendment #	Activity
01/27/1995	IND 43,693	#008	Response by Lilly noting that postal delays caused late receipt of annual report.
05/01/1995	IND 43,693		FDA letter to Lilly recommending that histological and reproductive toxicity studies be conducted.
06/05/1995	IND 43,693	#009	ADME Report No. 10 "A Plasma Concentration of LY246736 Dihydrate to DC-Mice" (Study No. M08894).
01/08/1996	IND 43,693	#010	Annual report for the period ending 11/10/95 period, noting that reproductive toxicity studies and other non-clinical studies had been conducted during the year. The report notes that "No clinical work on LY246736 has been conducted in the last year, and no further work is planned at this time. The decision to suspend further development was based on a reassessment of overall sponsor research goals. Barring transfer of the IND to another sponsor, Lilly will be considering withdrawal of the IND in the next year."
11/05/1996	IND 43,693		Date of Agreement between Lilly and Roberts, granting Roberts the right to develop LY246736 Dihydrate Capsules, as noted in Lilly letter of February 3, 1997.
11/20/1996	IND 43,693		Information Amendment: Pharmacology/Toxicology. [Submission of Tox Report No. 14]
01/08/1997	IND 43,693		Annual Report for 11/10/95 – 11/9/96 period stating, "No preclinical or clinical studies have been conducted during the past year and none are anticipated at this time."
01/21/1997			Receipt of Lilly Documentation by Roberts
02/01/1997	IND 43,693		Lilly transfers sole sponsorship of IND 43,693 to Roberts.
02/03/1997	IND 43,693		Notification to FDA of Lilly transfer of sole sponsorship of IND 43,693 to Roberts on November 5, 1996; that all records had been transferred to Roberts; and that there are no ongoing clinical trials at this time.
02/03/1997			Lilly's notice to FDA transferring IND to Roberts as of 2/1/97
02/12/1997	IND 43,696		Robert's notice to FDA accepting transfer of Lilly IND
02/12/1997	IND 43,696		Lilly letter to FDA providing information regarding February 3, 1997 transfer of all rights and obligations to IND 43,693 to the new sponsor, Roberts.

Date	IND/NDA	Serial or Amendment #	Activity
03/03/1997	IND 43,693		Lilly notification to FDA of transfer of sponsorship of IND 43,693 to Roberts Laboratories, a wholly owned subsidiary of Roberts Pharmaceutical Corporation, now Shire Pharmaceutical Group.
03/06/1997	IND 43,693		FDA response to letter of notification of 2/12/97 of transfer to Roberts.
03/12/1997	IND 43,693		Lilly letter to FDA committing to amend IND to cover any changes resulting from new ownership.
04/21/1997			Lilly ships 41 boxes of written materials to Roberts
04/25/1997			List of materials received by Roberts from Lilly on 04/24/97
08/18/1997			Lilly IND application archived at Roberts (6 volumes)
09/03/1997			Adolor Corp. Chemical Data Sheet: Adolor No. ADL-01-0261-6 (LY246736 (mu antagonist)
01/23/1998			Lilly ships 36 gm samples to Roberts
02/23/1998			Adolor identified LY246736 / Roberts in-licensing opportunity
03/12/1998			Adolor memo on LY246736 synthesis, formulation, clinical trials and safety issues.
03/12/1998			Adolor meeting at Roberts, discussing license to LY246736
03/31/1998	43,693		FDA request for annual report.
04/07/1998	43,693		Annual Report covering 2/1/98 – 4/7/98; Roberts states that the "last annual report that was prepared by Eli Lilly & Co. was submitted to the agency on January 6, 1995 for the review period ending November 10, 1994 (Serial No. 007)," and that "there has been no activity regarding this IND since Roberts acquired the rights to this product on February 1, 1997," and further stating that "there are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules." Roberts states, however, that "we wish to keep this IND in an active status in the event that Roberts initiates clinical trials with the drug."
05/20/1998			Adolor review of Phase 1 of IND application complete
05/21/1998			Lilly reevaluation of expired lots of LY246736 (5/11/98); letter to Roberts
05/26/1998			Continuing Adolor review of Lilly LY246736 dihydrate IND documents (at Adolor).

Date	IND/NDA	Serial or Amendment #	Activity
05/26/1998			Adolor discussion with Roberts about bulk drug manufacturing
05/28/1998			Lilly fax with results of re-analysis of LY246736 by Lilly
05/28/1998			Adolor internal discussions including clinical study design issues, doses, capsules
06/01/1998			Adolor discussions and transmittal of confidential disclosure to prospective manufacturer of capsules, requesting proposal for manufacture of 0.125, 1.0, 6.0 mg and placebo strengths.
06/01/1998			Contacted UPM again about the new Adolor project and their interest in manufacturing clinical supplies. (Also separately contacted PMRS.)
06/01/1998			Discussions & prep for due diligence visit
06/03/1998			Adolor visit to Roberts for review of documentation & samples
06/10/1998	IND 43,693		Adolor entered into an Option and License Agreement with Roberts for a sublicense of all rights for the development and commercialization of LY246736 (subject of IND 43,693)
06/24/1998	IND 43,693		Roberts letter to FDA authorizing FDA to refer to IND 43,693 on behalf of Adolor.
06/29/1998			Adolor telephone discussions with Lilly; confirmed Lilly did file Annual Report January 8, 1997 and requested two boxes of information from corporate storage; requested Lilly tox and drug metabolism information on urgent basis.
06/30/1998			Adolor telephone discussion with Roberts; Roberts will give letter of authorization to their IND for one year; Roberts requested that Adolor open own IND with own protocol, and refer to Roberts IND for preclinical/safety etc.; sponsorship cannot be transferred now, not until option period goes to full license.
07/01/1998			Schmidt telephone discussions including Roberts to fax authorization to Lilly to release data to ADL per license agreement.

Date	IND/NDA	Serial or Amendment #	Activity
07/07/1998			Arrangements finalized between Adolor and UPM to have UPM prepare GMP clinical supplies of ADL 8-2698; facsimile requesting Roberts to ship all materials listed in Roberts "Chemical Inventory for LY246736-Dihydrate Project" to UPM.
07/09/1998			Roberts ships 50+ samples of LY246736 & related materials to UPM on behalf of Adolor
08/03/1998	IND 56,553	#000	Adolor filed IND application for investigational drug ADL 8-2698 (Adolor's name for LY246736).
08/07/1998	IND 56,553		Letter from FDA confirming receipt of IND August 5, 1998.
09/01/1998	IND 56,553		FDA telephone contact regarding need for CMC information, which is not available, and discussion of options regarding IND submission options, withdraw, inactivate or clinical hold.
09/02/1998	IND 56,553	#001	Phone Call to request review date if IND was withdrawn or inactivated so CMC info could be sent; Adolor agrees to inactivate and resubmit with CMC data; follow letter to FDA.
09/02/1998	IND 56,553	#002	Adolor request for inactive status for IND 56,553
09/22/1998	IND 56,553		FDA letter placing Adolor IND 56,553 on inactive status.
10/06/1998	IND 56,553	#003	Adolor letter: Request reactivate and list of modifications to IND
10/23/1998	IND 56,553		FDA letter referring to letters of 09/22/98 and 10/6/98, accepting IND with statement that clinical trials can begin 30 days from receipt (October 7, 1998) of request to reactivate
12/17/1998	IND 56,553	#004	Protocol Amendment: Change in Protocol regarding 98-CP001 "An Ascending Dose Safety Study of ADL 8-2698 (LY246736) in Humans."
03/03/1999	IND 43,693		Roberts annual report noting no activity conducted under IND 43,693 during the report period of April 8, 1998 through September 30, 1998
04/06/1999	IND 56,553	#005	Protocol Amendment: New Protocol regarding 99-CP006 "A Phase I Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
05/24/1999	IND 56,553	#006	Protocol Amendment: New Protocol/New Investigator regarding 99-CP007 "A Phase I, Double-Blind, Placebo-Controlled, Dose Ranging Study . . ."

Date	IND/NDA	Serial or Amendment #	Activity
06/14/1999	IND 56,553	#007	Protocol Amendment: New Protocol/New Investigator regarding 13C109 "A Double-Blind, Randomized Placebo-Controlled Study of the effect of ADL 8-2698 on Opioid . . ."
06/17/1999	IND 43,693		Roberts letter to FDA authorizing FDA to refer to IND 43,693 on behalf of Adolor.
07/12/1999	IND 56,553	#008	Protocol Amendment: New Protocol/New Investigator regarding 99-CT002 "A Phase II Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
08/17/1999	IND 56,553	#009	Protocol Amendment: Change in Protocols regarding RC-99-CT001 "A Phase I Study Assessing Use of a Peripherally Selective μ Opioid . . ."
08/24/1999			Transfer of all LY246736 documents to Adolor
10/11/1999	IND 56,553	#010	Annual Report covering the period of October 7, 1998 to September 1, 1999, including updates on Phase 1 and 2 studies conducted during the year.
10/15/1999	IND 56,553	#011	Protocol Amendment: Change in Protocols regarding RC-99-CT002 "A Phase II Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
11/23/1999	IND 56,553	#015	IND Safety Report.
12/01/1999	IND 56,553	#012	New Protocol/New Investigator regarding 13C206 "A Phase II Double-Blind, Placebo-Controlled, Parallel Study of Efficacy . . ."
12/03/1999	IND 43,693	#020	Roberts letter to FDA withdrawing IND 43,693, noting that "the investigational drug has been licensed to ADOLOR Corporation . . . and will be researched under the ADOLOR Corporation's IND application;" and confirming that "there has been no activity regarding IND 43,693 since Roberts acquired the rights to this product from Lilly on February 1, 1997, and that there are no ongoing clinical trials and no patients are on therapy.
01/13/2000	IND 56,553	#013	Protocol Amendment: New Protocol/New Investigator regarding Protocol 13C208 regarding "A Phase II, Multicenter, Double-Blind, Randomized, Placebo-Controlled . . ."
01/19/2000	IND 56,553	#040	Request for End of Phase II Meeting – CMC.
02/01/2000	IND 56,553	#014	Protocol Amendment: New Protocol/New Investigator regarding Protocol 13C111 "Phase I Randomized, Double-Blind, Placebo-Controlled, Crossover . . ."

Date	IND/NDA	Serial or Amendment #	Activity
02/28/2000			Transfer of LY246736 documents from Roberts to Adolor
03/08/2000	IND 43,693		Telephone contact from FDA regarding "Withdrawal of Original Lilly IND (43,693) by Roberts Serial Number of SAE"
03/13/2000	IND 56,553	#016	Protocol Amendment: Change in Protocols regarding 13C206 Amend. 2: "A Phase II, Double Blind, Placebo-Controlled, Parallel Study of Efficacy . . ."
03/16/2000	IND 43,693		Telephone contact from Maryann Cherubini (MC), Clinical Program Director, to Alice Kacuba (AK), CSO-FDA, regarding "Transfer of Original Lilly IND (43,693) to Adolor."
03/22/2000	IND 43,693	#021	Roberts letter to FDA transferring all rights to IND 43,793 to Adolor, noting that there has been no activity regarding IND 43, 693 since Roberts acquired the rights to this product from Eli Lilly & Company on February 1, 1997; that there are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules under this IND; and that the last Annual Report was submitted to the IND on March 3, 1999.
03/29/2000	IND 43,693	#022	Adolor Letter accepting all agreements, promises and conditions made by Roberts that were still in effect at the time of the transfer.
04/13/2000	IND 56,553	#017	Protocol Amend: New Protocols etc., regarding 13C212 "Force Titration – Chronic Methadone Therapy for Opioid Addiction . . ."
06/09/2000	IND 56,553	#018	Protocol Amendment: Change in Protocol regarding 13C208, "Single Dose, Chronic Opioid Therapy for Pain or Opioid Addiction . . ."
07/13/2000	IND 56,553	#019	Request for Type B Meeting
07/13/2000	IND 56,553	#020	Information Amendment regarding "A Chronic Tox Study in Fischer 344 Rats Given LY246736 Dihydrate . . ."
08/07/2000	IND 56,553	#021	Protocol Amendment: New Protocol etc. regarding 13C214 "Postoperative Opioid-Induced Bowel Dysfunction . . ."
09/06/2000	IND 56,553	#022	Information Amendment regarding Protocol 13C109.
09/12/2000	IND 43,693	#023	FDA letter to Adolor requesting further information to complete change in sponsorship of IND 43,693.

Date	IND/NDA	Serial or Amendment #	Activity
09/13/2000	IND 56,553	#023	Pre-Meeting Package (Briefing Document).
09/21/2000	IND 43,693		Adolor letter to FDA providing requested information regarding transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, noting, *inter alia*, that investigational compound LY246736 Dihydrate Capsules was licensed to Adolor for development; that Adolor filed its own IND 56,533, which is currently active and refers to the investigational drug as ADL 8-2698; that Roberts' (formerly Lilly's) IND 43,693 was referenced in Adolor's IND filing; and that any relevant sections and reports from IND 43,693 will be filed in the NDA.
10/03/2000	IND 56,553	#024	Information Amendment: Final Clinical Study Report.
10/03/2000	IND 56,553	#025	Protocol Amendment: New Protocol etc. regarding 13C213 "A multicenter Phase II/III, Double-Blind, Dose Ranging, Placebo-Controlled . . ."
10/03/2000	IND 56,553	#026	Information Amendment; CMC, regarding CMC Request for Comments.
10/16/2000	IND 56,553	#030	Adolor and FDA face to face meeting to discuss clinical development plan and proposed endpoints of study; facsimile including slides from meeting, slides assigned serial #030
10/26/2000	IND 56,553	#027	Information Amendment: Clinical Protocol Amendment, to provide for a revised clinical investigator's brochure etc.
11/15/2000	IND 56,553	#028	Protocol Amendment; "New Investigator information for protocol 12C213. . ."
11/15/2000	IND 56,553	#029	General Correspondence; New Corporate Address for Adolor
12/14/2000	IND 56,553	#032	Protocol Amendment: Change in Protocol 13C214; "Addition of Daniel Paulson, MD to Protocol . . ."
12/19/2000	IND 56,553	#033	Request for Special Protocol Assessment.
12/19/2000	IND 56,553	#034	Information Amendment: Clinical: Statistical Analysis; "The submission of statistical analysis plans for a pivotal trial and a final clinical study . . ."
12/21/2000	IND 56,553	#035	Information Amendment: Pharmacology/Toxicology: Final Study; "Submission of two drug disposition studies, one in the rat and one in the dog . . ."

Date	IND/NDA	Serial or Amendment #	Activity
12/21/2000	IND 56,553	#036	Information Amendment: Chemistry; including "Amending the subject IND to provide for the submission of data on a new manufacturer . . ."
01/04/2001	IND 56,553	#037	Annual Report, including updates on Phase 1 and 2 studies conducted during the year
01/04/2001	IND 56,553	#038	Press Release of Phase II trial results of studies with ADL 8-2698 in opioid bowel dysfunction.
01/19/2001	IND 56,553	#039	Request for End of Phase II Meeting with the Division for ADL 8-2698.
02/09/2001	IND 56,553	#041	End of Phase II CMC Pre-Meeting Package.
02/09/2001	IND 56,553	#042	End of Phase II Pre-Meeting Package (Briefing Document).
02/09/2001	IND 56,553	#043	Protocol Amendment: New Protocol, New Investigators, including "Submit new protocol under trial #14C302. Also submitted new investigators . . ."
03/02/2001	IND 56,553	#044	General Correspondence, including disk with revised list of attendees.
03/13/2001	IND 56,553		End of Phase II Meeting for ADL 8-2698.
03/22/2001	IND 56,553	#045	Minutes from the End of Phase II Meeting for ADL 8-2698.
04/11/2001	IND 56,553	#048	Protocol Amendment: New Protocol/New investigators; Amended IND to include a new Protocol 13C217.
06/14/2001	IND 56,553	#052	Protocol Amendment: Change in Protocol; Change in the statistical section of Protocol 13C217.
07/05/2001	IND 56,553	#059	Response to FDA Request for Information.
08/21/2001	IND 56,553	#065	Response to FDA Request for Information.
11/13/2001	IND 56,553	#073	Information Amendment: Chemistry, Manufacturing & Controls; Request for Comment
12/04/2001	IND 56,553	#031	General Correspondence: "Response to Division minutes from our October 16, 2000 meeting."
12/05/2001	IND 56,553	#077	Information Amendment: Clinical (Statistical Analysis Plans for Phase III Protocols.
01/15/2002	IND 56,553	#088	Annual Report, including updates on clinical studies conducting during the year
03/01/2002	IND 56,553		Adolor and FDA face to face meeting to continue discussions on development plan
04/09/2002	IND 56,553	#099	Minutes of Meeting with Division (March 1, 2002)

Date	IND/NDA	Serial or Amendment #	Activity
06/07/2002	IND 56,553	#104	IND Safety Report: Initial Written Report
09/05/2002	IND 56,553	#113	Protocol Amendment: Change in Protocol, Information Amendment: Clinical
10/03/2002	IND 56,553	#118	Information Amendment: Clinical; Submitted a Final Clinical Study Report 13C214 to the IND
12/16/2002	IND 56,553	#130	Information Amendment: Pharmacology Toxicology
01/06/2003	IND 56,553	#134	Annual Report, including updates on Phases 1, 2, and 3 studies conducting during the year
03/17/2003	IND 56,553	#143	IND Safety Report: Follow-up to a Written Report
08/01/2003	IND 56,553	#154	Information Amendment: CMC; Microbial issue
12/16/2003	IND 56,553	#172	Clinical: Statistical Analysis Plan Addendum
01/05/2004	IND 56,553	#177	Annual Report for 2003
02/13/2004	IND 56,553		FDA Letter granting Fast-Track Status Approval
02/23/2004	IND 56,553		Adolor and FDA face to face meeting to discuss NDA submission
02/25/2004	IND 56,553		Adolor and FDA face to face meeting to discuss CMC section of NDA submission
04/30/2004	IND 56,553		Telephone call from FDA granting Adolor request to file the NNDA under the Pilot 1, Continuous Marketing Application program.
05/04/2004	IND 56,553		NDA Pharm/Tox Submitted under CMA Pilot 1 Program as Reviewable Unit #1
05/27/2004	IND 56,553		NDA CMC Submitted under CMA Pilot 1 Program as Reviewable Unit #2
06/25/2004	NDA 21,775		Full NDA Submission
09/07/2004	NDA 21,775		Letter from FDA accepting NDA for review and defining PDUFA date as 4/25/05
09/24/2004	NDA 21,775		NDA Amendment #1 – change of address for Drug Product Packager
10/22/2004	NDA 21,775		NDA 120-Day Safety Report
01/10/2005	IND 56,553	#214	IND Annual Report
01/20/2005	NDA 21,775		Submission of Request for Meeting to discuss GSK Study 001
01/24/2005	NDA 21,775		FDA Request for Clinical Pharmacology Information
01/26/2005	NDA 21,775		Submission of Response to Request for Information: Clinical Pharmacology

Date	IND/NDA	Serial or Amendment #	Activity
01/28/2005	NDA 21,775		NDA Amendment #2 – Submission of GSK Study 001 Clinical Data
01/28/2005	NDA 21,775	Amendment #002	Submission of GSK #001 study data
02/14/2005	NDA 21,775		Submission of Briefing Document for 3/16/2005 meeting
03/3/2005	NDA 21,775		FDA Letter acknowledging Reviewable Unit 003 as an error and acknowledging the full NDA was received June 25, 2004.
03/14/2005	NDA 21,775		Receipt of FDA responses to Adolor's questions for 3/16/2005 meeting
03/16/2005	NDA 21,775		FDA/Adolor Face-to-Face Meeting
04/08/2005	NDA 21,775	Amendment #003	Submission to NDA of Final Clinical Study Report for GSK #001
04/18/2005	NDA 21,775		Receipt of FDA Meeting Minutes for 3/16/05 face-to-face meeting
04/19/2005	NDA 21,775		FDA letter postponing PDUFA date by 90 days due to Major Amendment #003
04/21/2005	NDA 21,775		Submission of Briefing Document for 5/24/2005 meeting to discuss statistical methodology (meeting did not occur)
05/19/2005	NDA 21,775		Response to Request for Information: Clinical Pharm (request received in email)
05/26/2005	NDA 21,775		Response to Request for Information: Clinical Pharm and Biopharm (request received in fax)
06/01/2005	NDA 21,775		Response to Request for Information: Biopharmaceutics Information (request received in email)
06/20/2005	IND 56,553	Serial #227	Submission: Protocol Amendment: Change in Protocol, New Investigator
07/14/2005	NDA 21,775		Submission of Response to Request for Revised Indication in the NDA labeling
07/21/2005	NDA 21,775		FDA Action Letter to NDA, "Approvable"
07/22/2005	NDA 21,775		Submission of Response to Action Letter and Request for Meeting to discuss content of Adolor's complete response letter
07/25/2005	NDA 21,775		Receipt of FDA Request for Clinical Pharmacology and Biopharmaceutical Data (Pop PK analyses).

Date	IND/NDA	Serial or Amendment #	Activity
08/05/2005	NDA 21,775		Receipt of FDA Confirmation of 9/7/2005 Face–to-Face Meeting
08/17/2005	NDA 21,775		Submission of Desk Copy to Project Manager of 7/22/2005 submission
08/22/2005	NDA 21,775		Submission of Briefing Document for 9/7/2005 Face-to-Face Meeting
09/07/2005	NDA 21,775		FDA/Adolor Face-to-Face Meeting for discussion of complete response to action letter
09/20/2005	IND 56,553	#230	Submission: Protocol Amendment: New Investigator
10/06/2005	NDA 21,775		FDA Letter received regarding endpoint discussion for Study 314
10/14/2005	NDA 21,775		Submission of Statistical Analysis Plan for Complete Response
10/24/2005	NDA 21,775		Receipt of FDA letter requesting Opioid consumption analyses
11/04/2005	NDA 21,775		Submission of Response to Request for Information (opioid consumption analysis)
11/20/2005	IND 56,553	#232	Submission: Protocol Amendment: New Investigator
12/15/2005	NDA 21,775		Receipt of FDA Letter of Comments to the Statistical Analysis Plan submission
12/19/2005	NDA 21,775		FDA/Adolor Telephone Conference re Complete Response
01/16/2006	NDA 21,775		Submission of Statistical Analysis Plan for Study 14CL314 and NDA Complete Response
01/31/2006	NDA 21,775	Amendment #004	Submission of CMC to cover 12 mg capsules and updated methodology
02/09/2006	IND 56,553	#241	Submission: Protocol Amendment: New Protocol, New Investigator
02/24/2006	NDA 21,775		Submission of FDA Requested Clinical Pharmacology and Biopharmaceutical Data (request from FDA 7/25/2005)
03/02/2006	IND 56,553	#244	Submission: Initial Safety Report - GSK SAE
03/22/2006	IND 56,553	#246	Submission: Information Amendment: CMC
04/10/2006	IND 56,553	#248	Submission: Safety Report: Follow-up GSK SAE
04/20/2006	IND 56,553	#250	Submission: Protocol Amendment: New Investigator
05/09/2006	NDA 21,775		Resubmission of NDA (submission of Complete Response to Action Letter)

Date	IND/NDA	Serial or Amendment #	Activity
06/07/2006	NDA 21,775		Submission of minor amendment to Complete Response (updated 2 tables)
06/15/2006	IND 56,553	#258	Submission: Protocol Amendment: New Investigator
07/12/2006	NDA 21,775		Letter to FDA Requesting 90 Day Review Meeting
07/27/2006	NDA 21,775		Fax from FDA - 90 Day Review Meeting Granted
08/17/2006	NDA 21,775		To FDA Briefing Document re 9/18/06 Meeting
08/18/2006	IND 56,553		Letter Received from FDA – Combined Annual Report Granted
08/23/2006	NDA 21,775		Letter Received from FDA – Information Request – Refer to June 25,2004 NDA
09/06/2006	NDA 21, 775		Letter Received From FDA – Information Request Letter
09/08/2006	NDA 21,775		Fax Letter from FDA – Information Request, Per BioPharm Reviewer
09/13/2006	NDA 21,775		Letter to FDA Response to Request for Information, Labeling
09/14/2006	NDA 21,775		Email from FDA – Meeting Response – 90 Day 2nd Cycle Meeting
09/15/2006	NDA 21,775		Response to Information Request – Clinical Pharmacology
09/21/2006	NDA 21,775		Response to Information Request of 9/18/06 Meeting
09/25/2006	NDA 21,775		Fax Request from FDA – Information Request Additional Clinical and Statistical Data
09/27/2006	NDA 21,775		Response to FDA re Information Request of September 25, 2006
10/03/2006	NDA 21,775		Fax Request from FDA – Information Request – Summary of CV Events in POI
10/04/2006	NDA 21,775		Letter and Listings to FDA in response to Information Request of 10/03/06– Summary of CV Events in POI
11/06/2006	NDA 21,775		Letter to FDA – Response to Action Letter and Meeting Request
11/08/2006	NDA 21,775		FDA Letter Received Noting Receipt of Submission and Approvable
11/09/2006	NDA 21,775		Letter to FDA Requesting Face-to-Face Meeting re Approvable Letter of 11/3/06
11/17/2006	NDA 21,775		Letter from FDA Granting Meeting Request –Refer to Letter of 11/09/06 to FDA

Date	IND/NDA	Serial or Amendment #	Activity
11/21/2006	NDA 21,775		To FDA – Briefing Document
11/29/2006	NDA 21,775		Fax from FDA re Preliminary Responses to Questions included in 11/21/2006 Background Info for Post Action Meeting
01/18/2007	NDA 21,775		Letter to FDA -Response to Request for Information – Clinical Pharmacology
05/11/2007	NDA 21,775		Letter to FDA – Capsules and Telephone Conference
06/06/2007	IND 56,553		Letter from FDA – Full Clinical Hold
06/15/2007	NDA 21,775		Letter to FDA – Proposed Content of Complete Response
08/09/2007	NDA 21,775		Letter to FDA – Complete Response to Approvable Letter
08/10/2007	NDA 21,775		Letter from FDA – Requesting Bone Marrow Study/2-yr Carc for Complete Response
08/27/2007	NDA 21,775		Letter from FDA – Receipt on 8/10/2007of Response from 8/09/2007
09/12/2007	IND 56,553		Letter from FDA – Clinical Hold
10/09/2007	NDA 21,775		Letter from FDA – Information Request – Clinical Data
12/17/2007	NDA 21,775		Submission to FDA: Briefing Document
12/28/2007	NDA 21,775		Letter to FDA – Response to Information Request of 12/20/2007
01/17/2008	NDA 21,775		Letter from FDA - RiskMAP Proposal
01/17/2008	NDA 21,775		Letter from Executive CAC
02/08/2008	NDA 21,775		Letter from FDA – RiskMAP proposal received
02/28/2008	NDA 21,775		Letter from FDA - Mouse, Rat Carc Comments
03/05/2008	NDA 21,775		Letter to FDA – Response to Information Request – Study Report 13CL130
03/06/2008	NDA 21,775		Letter to FDA – Cystecomy Synopsis
04/04/2008	NDA 21,775		Letter from FDA – Advice Letter – Proposed Labeling
04/14/2008	NDA 21,775		Submission of Revised Proposed Labeling
04/15/2008	NDA 21,775		Submission of Pediatric Plan
04/15/2008	NDA 21,775		Submission of Revised Proposed Labeling Based on FDA Feedback from 4/14/2008 Teleconference
04/17/2008	NDA 21,775		Submission of Revised RiskMAP

Date	IND/NDA	Serial or Amendment #	Activity
05/01/2008	NDA 21,775		Correspondence to FDA. L. Young to D. Griebel. Per E-mail from M. Scherer 25- April-2008. Response to Information Request – Revised Carton and Blister Packaging
05/02/2008	NDA 21,775		Correspondence to FDA Per E-mail fm M. Scherer 2-May-2008: Response to Information Request – Final Draft Labeling (PI)
05/02/2008	NDA 21,775		Correspondence to FDA Per E-mail fm M. Scherer 29-Apr-2008: Response to Information request – Final Draft RiskMAP
05/06/2008	NDA 21,775		Telephone Contact: M. Scherer to L. Young regarding Marketing Exclusivity Request on Labeling Changes - Still on schedule for PDUFA date
05/09/2008	IND 56,553		Correspondence from FDA. J. Korvick to L. Young. Clinical Hold lifted
05/14/2008	NDA 21,775		Correspondence from FDA. J. Beitz to L. Young. Information Request – REMS Requirements
05/15/2008	NDA 21,775		Correspondence to FDA: Response to Information Request – REMS Submission
05/20/2008	NDA 21,775		Correspondence from FDA. J. Beitz to L. Young. Approval Letter

EXHIBIT 14

AUTHORIZATION TO ACT ON BEHALF OF ASSIGNEE IN APPLICATION FOR PATENT TERM EXTENSION

Eli Lilly and Company, a corporation created and existing under the Laws of the State of Indiana, represents that it is the record owner of United States Patent No. 5,434,171, by reason of an assignment from the inventors thereof recorded on February 15, 1995 at Reel 007343, Frame 0467, hereby authorizes the below named registered practitioner to act on its behalf before the United States Patent and Trademark Office and the United States Food and Drug Administration with respect to the Application for Extension of Patent Term Pursuant to 35 U.S.C. § 156 seeking the extension of U.S. Patent No. 5,434,171.

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Eli Lilly and Company

By: Douglas K Norman

Date: April 22, 2008

Douglas K. Norman
Print Name

Vice President and General Patent Counsel
Title